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In This Issue

The Biological Actions and Therapeutic Applications of the B-Chloroethyl Amines and Sulfides

Alfred Gilman and Frederick S. Philips

Science and Our Future

E. U. Condon

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DIMITRI IVANOWITCH MENDELÉEFF was born in Tobolsk, Siberia, February 7, 1834.

He earned his master's degree at the University of St. Petersburg (now Leningrad) in 1856 and his Doctor of Science degree some five years later, at which time he was appointed Professor of Chemistry at the Technological Institute. In 1866 he became Professor at the University. He resigned in 1890, and in 1893 was Director of the Bureau of Weights and Measures.

Mendeléeff is recognized as the principal author of the Periodic Law. He contributed to our knowledge of the properties of liquids, theories of solution, the development of the gas laws and the nature and origin of petroleum. He was one of the greatest teachers of his time.

His immortal paper on "The Relation of the Properties to the Atomic Weights of the Elements" was presented to the Russian Chemical Society in 1869. His prediction of the existence and properties of unknown elements was vindicated completely.

He died February 2, 1907.

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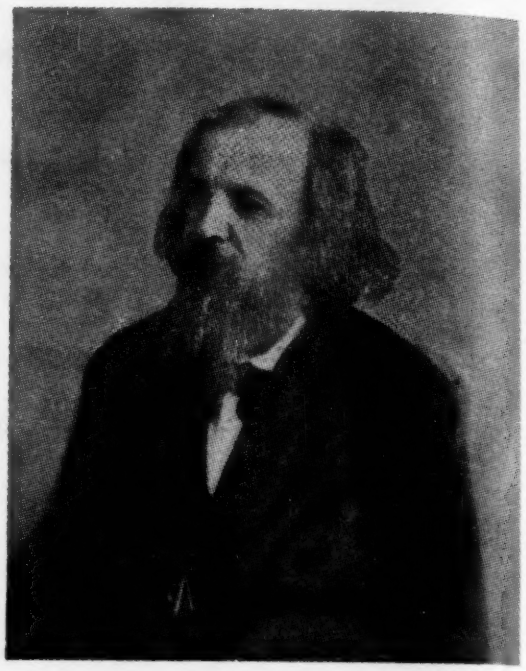

DIMITRI IVANOWITCH MENDELÉEFF
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The Biological Actions and Therapeutic Applications of the B-Chloroethyl Amines and Sulfides

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AT THE CONCLUSION OF WORLD WAR I the theory was generally accepted that mustard gas exerted its vesicant action by releasing hydrochloric acid intracellularly. A few isolated reports appeared describing remote systemic effects of mustard gas on hematopoietic tissues (*1–3*), the gastrointestinal tract (*3–5*), and electrolyte and fluid balance (*3*). Although in the interim between wars the adverse effects of mustard gas on leucopoietic tissues (*6–8*) and on the growth of experimental tumors (*9*) received some attention, biological research on chemical warfare agents remained relatively quiescent. With the advent of World War II research on war gases was resumed, and the newer knowledge and technics of a quarter of a century of scientific progress utilized. New compounds were proposed as potential offensive agents. Mustard, *bis*(β-chloroethyl)sulfide, shared interest with a series of nitrogenous analogues, *bis*- and *tris*(β-chloroethyl)-amines. It was appreciated early that the sulfur and nitrogen mustards were not only contact vesicants but, following absorption, could exert cytotoxic actions on a variety of tissues. Furthermore, cellular susceptibility to these compounds appeared to be related in a general way to the degree of proliferative activity.

With the conviction that only with an understanding of the basic mechanisms of cellular action could significant advances be made in the treatment of vesicant war-gas casualties, the study of the actions of the sulfur and nitrogen mustards on fundamental cell processes was pursued. These studies have revealed a type of action on cells which can be likened to that of no other chemical agent but which resembles in many ways that of X-rays. Cautious preliminary trials have also been made of the possible value of the nitrogen mustards in the treatment of neoplasms, in particular those of lymphoid tissue.

The fact that agents classified as "confidential" were involved in the above studies has heretofore precluded the possibility of presenting the results in the open literature. This report reviews briefly the contributions which have focused attention on the cellular actions of the mustard compounds and gives a general description of their systemic effects as well as a preliminary statement of their possible clinical applications. Because of space limitations important contributions of many investigators will have to go unmentioned.

Chemical Transformations and Reactions of the Nitrogen and Sulfur Mustards

The nitrogen and sulfur mustards owe their physiological activity to a basic chemical reaction which they share in common, namely, intramolecular cyclization in a polar solvent to form a cyclic onium cation with liberation of Cl^-. The reaction may be depicted as follows, Z representing the sulfur or nitrogen atom:

$$R\text{–}Z\text{–}CH_2CH_2Cl \rightarrow R\text{–}{}^{+}\overline{Z\text{–}CH_2CH_2} + Cl^-$$

The onium cation—ethylenimonium in the case of the β-chloroethyl amines, ethylenesulfonium in the case of β-chloroethyl sulfide—reacts readily with anions and various uncharged nucleophilic molecules. It is the great reactivity of the cyclic onium cation which imparts to this group of vesicants their varied actions.

The property of halogenated alkylamines to form cyclic onium cations was known before the war (*10–12*). With the introduction of *bis*- and *tris*(β-chloro-

This paper was prepared as a background for forthcoming articles on the clinical application of the β-chloroethyl amines with the approval of the following agencies: Medical Division, Chemical Warfare Service, United States Army; Division 9, NDRC, and Division 5, Committee on Medical Research, OSRD; Committee on Treatment of Gas Casualties, Division of Medical Sciences, NRC; and Chemical Warfare Representative, British Commonwealth Scientific Office.

ethyl)amines as chemical warfare agents, the importance of the formation of the reactive ethylenimonium ring was appreciated early. Moreover, the study of cyclization of β-chloroethyl amines led to appreciation of the existence of the analogous sulfonium cations. The present knowledge of the chemistry of the mustards, with respect to both the kinetics of cyclization and the reactions of the resultant onium compounds, has been the cooperative contribution of many groups of investigators (*13–22*) whose final publications in the open literature must be awaited. However, so important are the basic chemical findings for an understanding and explanation of the physiological actions of the nitrogen and sulfur mustards that a few pertinent facts will be reviewed here.

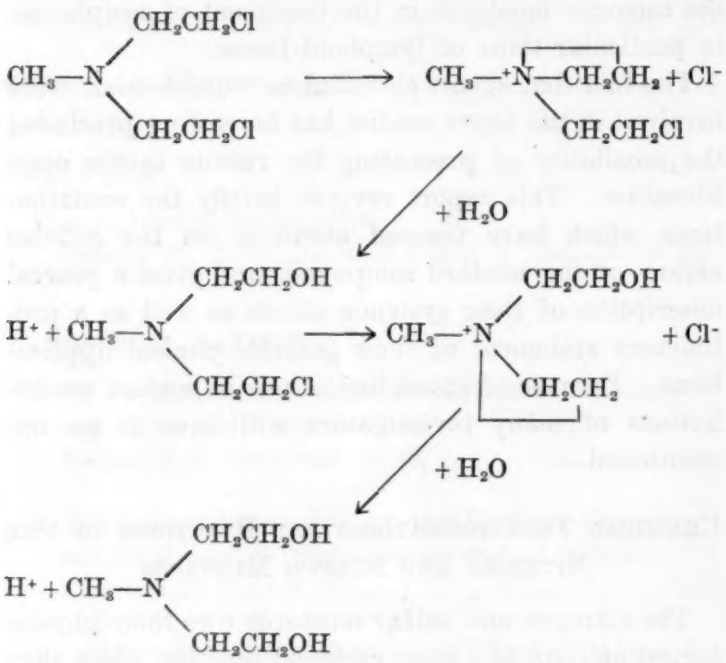

FIG. 1

Two basic distinctions may be made between the chemical behavior of the nitrogen and sulfur mustards. In the case of β-chloroethyl amines, cyclization cannot occur when a proton becomes coordinated with the nitrogen atom. Thus, solutions are stable in strong acid. Hydrogen-ion concentration does not affect the formation of the sulfonium ring. This distinction is of little importance at the pH of body fluids. Secondly, the reactivity of the ethylenesulfonium ring of mustard is so great that it never accumulates in solution in sufficient amount to permit its isolation. On the other hand, the various ethylenimonium compounds are, as a group, less reactive, and several have been isolated. In the case of the majority of the nitrogen mustards, this distinction is of greater chemical than physiological significance in that the reactivity of the ethylenimonium cation is ample to allow the compounds to produce toxic actions in general similar to those of sulfur mustard. For the most part, therefore, the nitrogen and sulfur mustards can be discussed together with respect to the basic relations between chemical structure and physiological actions.

As a prototype of the β-chloroethyl vesicants the behavior of methyl-*bis*(β-chloroethyl)amine may be considered. In dilute aqueous alkaline solution the series of reactions shown in Fig. 1 occurs. Side reactions involving polymerization may occur.

The majority of the nitrogen mustards are *bis*(β-chloroethyl)amines, the third valence of the nitrogen being occupied by one of a variety of alkyl groups. Inasmuch as the rate of cyclization and the activity of the ethylenimonium cation are influenced by substituent groups on the molecule, a large number of nitrogen mustards of different physicochemical and pharmacological properties is available. Thus, the scope of future investigations on the relations between chemical constitution and pharmacological action of the nitrogen mustards is wide.

In pure aqueous solutions at physiological hydrion concentrations the ethylenimonium or sulfonium cation reacts with H_2O. However, if other substances are present, they can react competitively. So reactive are some compounds that in their presence the reaction with water is negligible. Literally hundreds of compounds have been studied in this manner. The objective in many of these studies was the discovery of an effective antidote for the local and systemic actions of the mustards. More pertinent to the present discussion is the ability of ethylenesulfonium or imonium compounds to alkylate the functional groups of compounds of biological importance. Among these may be mentioned the α-amino, imidazole, sulfhydryl, sulfide, phenolic, ε-amino, and imino groups of amino acids and peptides; inorganic phosphate as well as glycerophosphate and hexose phosphates; the amino groups of adenosine and thiamine; and the pyridino-N of nicotinic acid amide and pyridoxine. The carboxyl and amino groups of numerous proteins which have been found reactive with sulfur mustard appear vulnerable to alkylation, although other functional groups are also involved. These proteins include hemoglobin, insulin, gelatin, crystalline egg albumin, tobacco mosaic virus, ovalbumin, silk fibroin, and protamine as well as various purified or crystalline enzymes to be considered below.

The implication that the systemic toxic action of the mustards is due to the reaction with any single compound listed above is not intended. However, the likelihood that the basic mechanism of the cytotoxic action of the mustards involves a similar reaction with a vital cellular constituent, possibly as yet unknown, is great.

Systemic Pharmacology and Pathology of the Mustards

The nitrogen and sulfur mustards elicit a variety of systemic pharmacological actions. For the most part these are prominent only after the administration of acutely lethal doses. Although the pattern of action of the compounds as a group is similar, certain distinctions are evident. Thus, the possibility exists that changes in chemical constitution can effect a specificity of action.

Cytotoxic action. The outstanding systemic action of the nitrogen and sulfur mustards is that which causes, in a manner still unexplained, the death of cells. The possible relationship between the action of the mustards on enzyme systems and their cytotoxic effects and the details of their more specific action on cell nuclei will be presented below. Pertinent to the present discussion is the relative susceptibility of the various tissues to this cytotoxic action. As a generalization, it may be stated that cellular susceptibility is related to proliferative activity. Thus the formed elements of the blood and the mucosa of the gastrointestinal tract first reflect the cytotoxic action of the mustards. The vulnerability of the blood-forming organs and the intestinal tract was realized as a result of investigations conducted during World War I, (*1–5*) and current studies on the nitrogen and sulfur mustards have contributed a wealth of new knowledge. Briefly, the action of the mustards on the blood-forming organs as reflected in the peripheral blood of both experimental animals and humans results in a lymphopenia, granulocytopenia, thrombocytopenia, and moderate anemia (*23–34*). The severity of the response is in direct relationship to the dose administered. Marked effects on hematopoiesis can be obtained with sublethal doses.

The effects of the mustards on the gastrointestinal tract are equally marked. Nausea and vomiting are evident within a few hours (*26, 35*). This may be a reflex response from the gastrointestinal mucosa or possibly the result of direct medullary stimulation. Diarrhea becomes evident within 24 hours and becomes progressively more severe. Both the vomitus and feces may contain blood. As a result of the loss of fluid and electrolyte from the gastrointestinal tract, marked changes in body water occur (*26, 35, 36*). Furthermore, there is evidence that the action of lethal doses of nitrogen mustards on the kidney may result in a polyuria and a renal wastage of extracellular electrolyte (*37*). A loss of intracellular potassium and water may also occur (*37*). Eventually, circulatory collapse ensues, a typical shock picture is observed, and the animals die of respiratory failure (*26, 35*).

Acute pharmacological actions. The acute pharmacological actions of the mustards are seen only after the administration of supralethal doses. Prominent among these are central nervous system excitation resulting in convulsions and acute death (*26, 28*), parasympathomimetic effects as evidenced by salivation, miosis, etc., followed by a parasympatholytic action (*26, 28, 38*). With subconvulsive doses of nitrogen mustard a progressive muscular paralysis, eventually resulting in death from paralysis of muscles of respiration, is a characteristic finding (*26, 28*).

Relationship between chemical constitution and pharmacodynamic action. A fact which has been pointed out by several investigators is that only those β-chloroethyl compounds which can form a cyclic onium cation are capable of exerting the typical actions described above. Moreover, the toxicity of the members of this series appears to be related to the chemical characteristics of the onium cation. Thus, the toxicity and leucotoxic activity of the nitrogen mustards and sulfur mustard have been correlated with both the reactivity of the onium cation (*26, 28*) and the rate of cyclization of the parent β-chloroethyl compound (*16*).

Pathology of systemic mustard poisoning. As might be expected from the above actions of the mustards, the outstanding pathological lesions produced by either nitrogen or sulfur mustards are found in the intestinal tract, bone marrow and lymphatic tissue (*23, 26, 27, 34*). The intestinal lesion progresses from vacuolization and nuclear swelling of the epithelial cells to eventual necrosis and desquamation with hemorrhage. Lymphoid tissue throughout the body is uniformly involved. Lymphatic fragmentation may be evident within 10 hours, leading to a persistent lymphatic atrophy for a number of days. In the bone marrow early changes include swelling and alteration in the staining reaction of hematopoietic cells and a disappearance of mitotic activity. Progressive depletion of the marrow follows, and eventually, almost complete aplasia results.

In Vitro and *in Vivo* Inactivation of Enzymes by the Mustards

The fact that the administration of the nitrogen and sulfur mustards to experimental animals results in widespread systemic intoxication naturally led to the concept that the agents inhibit certain basic metabolic functions which are vital to the maintenance of normal cellular activities. It was reasonable to expect, therefore, that a variety of cells and tissues poisoned by the mustards either *in vivo* or *in vitro* would evidence significant metabolic changes. It has, in

fact, been found that the oxygen consumption and glycolysis of a large number of cells and tissues are inhibited to varying degrees following exposure to the agents *in vitro* and in some instances *in vivo*.

One of the earliest observations which antedated the recent war showed that the addition *in vitro* of sulfur mustard to minced tumor tissue resulted in moderate reduction of oxygen consumption and marked depression of the aerobic and anaerobic glycolysis of glucose (*39*). The anaerobic glycolysis of minced brain and chick embryo tissue was similarly reduced. Similar effects were reported by English investigators to occur in mammalian skin following the application of vesicant doses of sulfur mustard (*40, 41*). It was also determined in early English work that the oxidation of pyruvate by brain brei was significantly inhibited by sulfur mustard (*42*). Later work confirmed the effects of this mustard on the oxidative and glycolytic activities of intact mammalian skin (*43*). Furthermore, the inhibition of the respiration of avian erythrocytes *in vitro* (*13*), of the respiration and anaerobic fermentation of yeast cells (*17, 44*) and of the respiration and glycolysis of isolated mammalian cornea (*45*) was also demonstrated. Following parenteral administration of lethal doses of sulfur mustard significant inhibitions of anaerobic glycolysis and respiration have been noted in bone marrow (*41*) spleen (*41, 43*), and thymus (*43*), as well as inhibition of glycogen synthesis in the liver and intestinal absorption of glucose (*43*).

Certain of the nitrogen mustards have also been shown to inhibit to varying degrees the respiration of isolated slices of such tissues as lymph node, bone marrow, spleen, brain, liver, and kidney (*43, 46*). Moreover, the utilization of pyruvate by kidney slices and the synthesis of urea by liver slices were found sensitive to nitrogen mustard *in vitro* as well as in animals which had been gassed with lethal doses (*43*).

The fact that diverse cells and tissues which had been subjected to the toxic effects of sulfur and nitrogen mustards evidenced marked metabolic defects has fostered the theory that the primary mechanism of action of the vesicants was the inactivation of essential cellular enzymes (*47, 48*). This view has been supported by extensive investigations with skin and other tissues, and in addition it has been postulated that primary inactivation occurs only in a special class of essential cellular enzymes, the phosphokinases, which are concerned with phosphate transfer to or from adenylic compounds (*41*).

The "enzyme-inactivation" theory of the mechanism of toxic action of the mustards served as the impetus for extensive investigations of the *in vitro* sensitivity of a large number of enzyme systems. Briefly, the enzymes or enzymatic systems studied included proteins containing iron, copper, and zi and flavin prosthetic groups; dehydrogenases; hydr lytic enzymes such as fumarase, urease, and inve tase; catalysts involved in the metabolism of gluco and in reactions concerned with phosphate transfe intracellular and extracellular proteolytic enzyme various oxidases such as those of pyruvic acid, asco bic acid, histamine, and choline; acetylcholine esteras ribonuclease, hyaluronidase, and carboxylase (*13, 1 17, 41–43, 49*). The majority of the enzymes prove only moderately sensitive or resistant to inactivatio by the mustards. Among the highly sensitive enzyme were hexokinase, creatine and pyruvate phosphokinase inorganic pyrophosphatase, adenylic acid deaminase chick pepsin, kidney pepsinase, and peptidases o serum and skin and lung. In addition, choline oxidase and acetylcholine esterase isolated from brain, were readily inactivated by the nitrogen mustards.

On the basis of the results obtained from studies of *in vitro* inactivation it is generally conceded that the phosphokinases as a group are highly susceptible to the mustards but share this sensitivity with other types of enzymes. In view of this finding, some doubt has been expressed concerning the possibility that the inactivation of phosphokinases *in vivo* represents the primary and specific mechanism of toxic action of the mustards, especially since no obvious correlation has been found between susceptibility of enzyme systems *in vitro* and *in vivo* (*49*).

At present it is not possible to present a final statement concerning the merits of the "enzyme-inactivation" theory of mustard intoxication. That some enzymes possess a high order of sensitivity to the agents *in vitro* cannot be questioned. Whether the inactivation of the same enzymes *in vivo* represents a primary step in the course of events leading to cell pathology is, however, open to serious question. The consensus of opinion of many investigators is that the specific chemical lesion responsible for the changes that eventually lead to cell death has not yet been defined by studies on the inactivation of enzymes. The difficulties attending the clarification of the characteristics of such a lesion are apparent in cytological studies of mammalian cornea (*45*) and yeast (*44*), where concentrations of the mustards below those which affect either respiration or glycolysis have been found to produce fundamental changes in mitotic activity.

Nucleotoxic Action of the Mustards

Although diverse systemic effects can be elicited in the mammalian organism by the administration of toxic amounts of the mustards, threshold doses evoke pathological changes only in cells and tissues which normally exhibit relatively high rates of proliferation

d growth. Considerable attention has been focused the morphological changes exhibited by such cells response to the mustards in the hope that such dies might provide a better understanding of the sic cellular disturbances involved. As a result it s been shown that the mitotic activity of a variety cells from representative unicellular, invertebrate, phibian, mammalian, and higher plant organisms peculiarly sensitive to inhibition by minimally fective doses. For example, mild exposure of yeast ltures to sulfur mustard can produce an immediate duction in growth rate which may be sustained at duced levels by several succeeding generations of aughter cells before recovery is apparent (*50, 51*). milarly, the early cleavage of the sea urchin egg inhibited or retarded by brief immersion of either e unfertilized egg or the early zygote in minimally ffective concentrations of the mustards (*52*). The xposure of young salamander larvae elicits an imediate cessation of growth which can be attributed o an inhibition of mitotic activity in the proliferatng regions of all the tissues of the embryo (*53*). Those cells in which mitotic activity has been completed at the time of exposure continue functional differentiation in a normal manner. Following direct application of threshold amounts of the mustards to the intact eye or after parenteral administration of minimal lethal doses, the corneal epithelium of mammals can be largely depleted of mitotic figures for a period of several days without visible evidence of concomitant cytoplasmic or nuclear damage (*54*). Moreover, for several days after the parenteral administration of doses sufficient to cause lymphopenia and granulocytopenia in rats, mitotic activity is decreased in lymphoid, myeloid, and erythroid cells of hematopoietic tissues which have escaped the initial destruction caused by the agents (*27, 34, 54*) as well as in the intestinal mucosa (*54*). Finally, the mitotic rate of regenerating cells following partial hepatectomy has been found to be significantly lowered by the intravenous injection of sulfur mustard (*55*). In this regard it is important to note that similar doses do not evoke visible pathological changes in normal, nonproliferative hepatic tissue.

The inhibition of mitosis caused by mild exposure to the mustards does not in itself imply a primary nucleotoxic action of the agents; in fact, the mitotic arrest appears to be confined to the resting phase of the mitotic cycle (*52, 54*). Cells in active mitosis at the time of exposure complete their division with the result that ultimately the inhibited tissue may become depleted of mitotic figures (*54*). However, evidence of a more direct toxic action on nuclear mechanisms is the appearance of extensive nuclear fragmentation in cells of the corneal epithelium which have been exposed to doses somewhat higher than those which effect only a mitotic inhibition (*54*). The nuclear fragmentation and resultant chaotic chromatin dispersal can be considered as a pathological and incomplete mitosis (*56*). More convincing of the association of mitotic arrest with primary nuclear damage are studies on the inhibition of mitosis of pollen grains following exposure of *Tradescantia* inflorescences to minimal concentrations of sulfur mustard (*57*). The fate of the treated cells was shown to vary with the extent to which chromosomal abnormalities were elicited. Thus, severe exposure in association with complete mitotic arrest caused multiple chromosome breaks resulting in fragmentation, pycnosis, and ultimate death of the cell. Mild exposure which prolonged the resting period of the pollen grains caused chromosomal breaks in many of these cells. If these were not too numerous or followed by translocation, they were transmitted to daughter cells in the subsequent mitosis as heritable chromosome abnormalities.

Perhaps the most significant demonstartion of specific nucleotoxic action has been obtained from observations on the profound disturbances produced by the mustards on the structure and function of chromosomes in *Drosophila melanogaster* (*58*). Exposure of both male and female adults to sublethal doses was found to reduce or suppress fertility through disturbances of miosis and mitosis in the gametogenesis of both sexes. However, following exposure of adult males to lower doses which did not reduce fertility unduly, the genetic analysis of the X-chromosomes revealed a high incidence of sex-linked lethals greatly in excess of the natural rate of mutation as well as a significant number of translocations and inversions. No other class of chemical agents has been shown to have such specificity of action on chromosomal mechanisms. Indeed in the past similar effects have been attained to the same degree only by the use of short-wave radiation (X-ray and ultraviolet).

That the mustards can exhibit a primary nucleotoxic action is attested by the above demonstration that in threshold doses they act directly on the intimate structure of chromosomes, without apparent influence on other cellular entities, to produce an inheritable chromosomal abnormality which can be reproduced indefinitely by normal processes of cell division and thereby transmitted from ovum to ovum through several successive adult generations. The precise mechanism whereby changes in the chromosome are effected, whether by direct chemical reaction with its component compounds or as the result

of structural instabilities induced by inactivation of intimately associated nuclear enzymes, is a subject of future investigation. Of possible importance in this regard are observations on the inactivation of the infectivity of the nucleoprotein tobacco mosaic (*20, 59*) and bushy stunt (*59*) viruses. Although reaction of the viruses with the mustards resulted in extensive inactivation, moderate exposure which did not appreciably reduce infectivity was not accompanied by significant increases in mutation. It has been shown that under the latter conditions the virus molecule sustained multiple reactions with mustard groups.

On the basis of the marked susceptibility of nuclear mechanisms it is provocative to associate the cytotoxic action of the mustards with primary disturbances of nuclear function. Even the necrotization of hematopoietic and intestinal cells of mammals following fatal intoxication might conceivably be considered the eventual outcome of a primary nuclear derangement. However, it must be pointed out that abnormalities which cannot be readily interpreted as arising from a primary nuclear intoxication have been reported to result from exposure of cells to the mustards. Thus, the response of avian erythrocytes or their nucleated ghosts to the swelling action of applied detergents was demonstrated to be highly susceptible to inhibition by prior immersion in dilute solutions of the mustards (*60*). The inhibition of swelling has been interpreted to result from a primary change in the properties of the cytoplasmic stroma. Similar observations obtained with suspensions of rabbit bone marrow and lung cells (*60*) indicate that the effect is not limited to the avian erythrocyte. Although the significance of this cytoplasmic change is not clear, it does represent one of the most sensitive cellular reactions so far demonstrated to result from exposure to the mustards. Similarly, the application of dilute solutions of sulfur mustard to *Nitella flexilis* caused a marked loss of turgor associated with a loss of the normal semipermeability of the surface films to electrolyte (*61*). Finally, cytoplasmic changes have been noted in response to minimally effective doses of the mustards under circumstances which have not permitted an exact analysis of the sequences of morphological events. Thus, concentrations which inhibit the growth of cultures of choroid and sclerotic chick tissue cause a simultaneous swelling of cytoplasmic fat globules (*62*). Similarly, in cultures of embryonic membrane bone the first signs of injury are evident in the mitochondria, which undergo marked structural changes (*63*). It may also be mentioned that ameboid movement of leucocytes and metamyelocytes in suspensions of rabbit bone marrow is readily inhibited in the presence of nitrogen mustard (*46*).

Clinical Applications

The marked effects of the mustards on lympho tissue, coupled with the finding that actively prolife ating cells are selectively vulnerable to the cytotox action of the mustards, suggested the therapeutic u of these compounds in the treatment of neoplasm of lymphoid tissue. Because of its undesirable phys cal properties and extreme chemical reactivity, sulfu mustard does not lend itself to parenteral administra tion. However, nitrogen mustards in the form o their hydrochloride salts are water-soluble, crystallin compounds, which can be readily dissolved in steril saline for intravenous administration. Experiment on transplanted lymphosarcoma in mice revealed tha dissolution of such tumors could be rapidly effecte although the dose required bordered on the toxic, an the tumor invariably returned (*64*). The first clinica trial of the nitrogen mustards (*65*) was conducted o a group of six patients in the terminal stages o various neoplastic diseases. In two cases of lympho sarcoma in which X-ray therapy had been discon tinued, a rapid dissolution of large tumor masse followed a course of injections. The results were sufficiently encouraging to warrant further clinical experimentation. To date approximately 150 patients have been treated by several groups of investigators (*66–68*). For the most part observations have been limited to selected cases of Hodgkin's disease, lymphosarcoma, and leukemia. The findings may be summarized in general terms. The most favorable effects have been obtained in patients with Hodgkin's disease. Remissions characteristic of those which follow careful X-ray therapy have been observed. Symptoms were quickly alleviated, and physical evidence of lymphadenopathy, splenomegaly, and hepatomegaly regressed. It was necessary to repeat treatment at intervals varying from one to eight months. Less favorable results have been obtained in cases of lymphosarcoma. The response in acute and chronic lymphogenous and myelogenous leukemias has been disappointing.

The action of the available nitrogen mustards on lymphoid tissue has not yet reached that degree of specificity which precludes undesirable actions on the hematopoietic system. At present, dosage is limited by the occurrence of moderate granulocytopenia, thrombocytopenia, and anemia. However, if care is taken with dosage, an adequate clinical response may be obtained without affecting to a serious degree the formed elements of the blood. In addition, nausea and vomiting are very likely to occur for a brief period after each injection. No other undesirable effects on the gastrointestinal tract have been observed.

Comments.- Although some patients receiving ni-

gen mustards have been observed for a period of months, the evaluation of the clinical status of is group of compounds will require many more ars of careful study. At present there is no basis assuming that the therapeutic efficacy of the rogen mustards is any greater than that of X-ray. It is possible that the potential value of the nitro- n mustards in the treatment of neoplastic diseases ll be fully realized only when the opportunity to plore the relationship between chemical constitu- n and pharmacodynamic action has been exhausted. present only two of the nitrogen mustards have en investigated clinically, namely, *tris*(β-chloro- hyl)amine and methyl-*bis*(β-chloroethyl)amine. hese have been the product of a screening program designed for the evaluation of toxic chemical warfare agents rather than of compounds of therapeutic interest. Literally hundreds of congeners remain to be synthesized and evaluated. Thus, a series of compounds which can reproduce in many ways the cellular effects of X-rays is available for chemical and biological investigation. It may be hoped that the previous successes which have characterized the evolution of chemotherapeutic agents by chemical alteration of a parent compound may be duplicated in the case of the β-chloroethyl amines. The result would be a compound having a sufficiently specific toxic action for certain types of proliferative cells to possess therapeutic value.

(See p. 436 for list of references.)

Science and Our Future

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THE WAR'S DESTRUCTION FAR EXCEEDS that of any catastrophe yet known. The war ended with the application of a new weapon hat is a thousand times more frightful than the eapons which produced most of the war's frightulness. And already we have responsible statements rom scientists who effected this development that ombs a thousand times more powerful than those lready used are capable of being made in the near uture. There are men living who know how to make single bomb whose destructiveness is equal to a million ten-ton blockbusters. One such bomb, dropped on Washington or any other major city, may be expected to wipe out its population, to destroy its buildings utterly, and to render the site uninhabitable due to poisoning by radioactive materials.

In the face of this situation, people react essentially in one of two ways. One group says: "It's just another weapon. Mankind learned to adapt to the long bow, and the cross bow, and the B-29. We have always had wars." An extreme expression of this kind is found in a speech delivered in Philadelphia last December by Prof. Leslie A. White, of the Anthropology Department of the University of Michigan, who said: "As for the extermination of the human race as a consequence of hurling atomic thunderbolts, this too may be admitted as a possibility, and all we can say is that if it is to come, it will come." This is indeed a rather coldly hopeless, fatalistic expression. Prof. White further says: "Extravagant expressions of horror will not alter the course of events."

There is a certain rhetorical trick here in that, in our language, "extravagant" connotes exaggeratedly inaccurate, and thus emotionally detracts from the serious warnings which responsible physicists are trying to give us. I would agree that expressions of horror *alone* will not alter the course of events. But I insist that if we look at what civilization has suffered in World War II, even before the atom bomb, and couple it with the picture of a war with plentiful use of the old-fashioned "one-hoss shay" atom bombs, and further with the picture of a war with both sides equipped with the really potent 1950 models—then no expression of horror of which our hearts are capable can be exaggerated or extravagant. We need not, and should not, fatalistically await death, reading papers to an academic society meeting in a museum in Philadelphia.

The second kind of people react differently. We say: "This is the end." Mankind has brought down suffering and death on its head, spiritual values have been destroyed, hatreds have been nourished and developed into great social cancers by war, war fears, and war suspicions and divisions among men.

From an address delivered 5 March 1946 in Washington, D. C., **at the conclusion of the Fifth Annual Science Talent Search (*Science*, 1946, 103, 336). The guests for the evening were the 40 winners from the Science Clubs of America who received the Westinghouse Scholarships and scientists from the Washington area. The event was arranged by Science Service, whose director, Watson Davis, served as toastmaster.**

This has been going on since the beginning of time and will surely destroy us all if we let it continue. This second kind of people say simply that this must stop. We say there is such a thing as progress toward a higher level of development. With all the stumbling and fumbling, we see an upward trend throughout human history. We read the lesson of history to be that men can go forward together, and that men can progress to new freedoms and new areas of social adjustment.

We see that man's growing mastery over the forces of nature also serves to amplify the magnitude of the social crises which confront him. Centuries ago, wars were local affairs; however terrible, they affected only relatively small sectors of civilization. But the last two major wars were world wars in a true sense. Their damage literally affected everyone. We face a situation in which a future world war, employing atom bombs, rockets guided by radio, and many other marvels of man's perverted ingenuity, will achieve a destructiveness thousands of times greater than ever achieved before. The magnitude of the crisis is such that we must soberly think of the choice as being between drifting into a war which will lead to the destruction of civilization, leaving a remnant of stunned, confused, poverty-stricken, frightened men and women amid the ruins, or a wholesome healthy development of a united mankind, using its intelligence cooperatively for the good of all.

I beg of you, cast in your lot with the persons of the second kind—those who believe there is a possibility that men throughout the world can live in freedom and justice, in love and good will, that they can devote their full energies to constructive application of the rational thinking to call science to the arts of peace. In asking you to join with us, I make no promise of certain security. I only promise hope and tell you that the other way leads to certain doom. If we try to establish the brotherhood of man on earth, we may fail, but if we do not even try, we shall surely fail—and what an unbearable load of guilt our consciences will then have to carry!

So much for the generalities of the situation in which we find ourselves. Now I would like to comment a little more specifically on the immediate choices which lie before us.

We must assert ourselves in every kind of agency of world cooperation toward positive, wholesome working-together for human welfare. This means the fullest kind of active support to the efforts of peoples everywhere to go forward, in political and economic freedom, to the highest level of educational, scientific, and cultural achievement. This means, specifically, support to UNO, UNRRA, UNESCO, and whatever other such activities lie ahead.

We must particularly seek to bring about clo working relationships with our friends and allies, Russians. Russia and the United States are today most powerful nations in the world. Unless we get along together, there is no hope for peace. must seek to recapture something of the feeling joy and pride we had in being on their side, af Stalingrad and during their long, arduous drive push the Nazi war machine out of their devasta lands. We must welcome their scientists to our lab ratories, as they have welcomed ours to theirs, a extend the base of scientific cooperation with this gre people. Of course, we must behave this way towa the scientists of all nations—I only mention Russ because she is right now the target of attack by tho irresponsibles who think she would be a suitable a versary in the next world war.

We must regain for all scientists that freedom fro military domination which is so necessary if scien is to be used for peaceful ends. With Nazism n wholly exterminated, we must have scientists contri uting to the development of our tools of war, sin we may, if all else fails, have to use them. But t scientific life of the country must not be subord nated to, or derive its chief support from, the mil tary.

This is essential in the interests of the militar themselves. Because the scientific spirit is so com pletely opposite to the military spirit, science simpl will not go forward under domination. Nowadays me must work together in large organizations. It is char acteristic of the military organization that operations are planned and directed from the top, with the details executed by men below, by persons who unquestioningly and obediently respond to the orders given them from above. The flow of original thinking is from the top to the bottom. I conceive just the opposite to be true in a properly administered scientific organization. The function of a scientific director is to set up working conditions where the lowliest novitiate is put in touch with all the problems in his field and encouraged to worry about them and to come out creatively with new ideas and results. He is the sole judge of what knowledge he needs in order to work effectively on his problem. The flow of original thinking in this case is mainly from the bottom to the top. Every worker must have access to the whole story because no one can foresee which scientist will have the truly creative idea. And each scientist must be free to discuss his ideas, while in the formative state, with his colleagues anywhere, for it is from the working together of many minds that new science comes.

In contrasting the military and scientific, I do not wish to imply that one is wholly wrong and the other wholly right. Just as I do not recommend the mili-

y procedure for the conduct of scientific research, ither would I want our safety to depend on the tcome of a battle in which the scientific method of e discussion, independent thinking, and mutual ticism was followed by all the captains and lieu- nants on the battlefield. Military operations and ientific research are two quite different kinds of man activity, and neither should be subordinated to e other.

Of course, my reason for stressing this point is that ght now we are confronted in America with a situa- on in which scientists are being held very strictly der military domination, to the severe detriment our scientific development and the development of holesome international relations.

What is going on? Prominent scientists are denied e privilege of traveling abroad. Physicists are not llowed to discuss certain areas of their science with ch other, even as between individuals working on losely related phases of the same subject. They can mmunicate only through official channels involving nsorship of their communications by army officers ithout knowledge and so without competence. In- ormation essential to understanding is being denied o students in our universities, so that, if this situa- ion were to continue, the young students we honor here tonight will get from their professors only a watered-down army-approved version of the laws of nature.

In this connection one is reminded of the eighteenth verse of the eighth chapter of *Ecclesiastes,* where we read: "Wisdom is better than weapons of war; but one sinner destroyeth much good."

Some seem to think that the laws of nature are ours exclusively, and that we can keep others from learning by locking up what we have learned in the laboratory and not telling it to our allies. Later they will learn what we know—and more which, because of our unfriendly behavior, we cannot expect them to tell us. In the course of time, because of such provocations, we are allies no more—we start as friends and end as snarling, suspicious neighbors.

It is sinister, indeed, how one evil step leads to another. Having created an air of suspicion and mistrust, there will be persons among us who think other nations can know nothing except what is learned by espionage. So, when other countries make atom bombs, perhaps much better than those we have, these persons will cry "Treason!" at our scientists, for they will find it inconceivable that another country could make a bomb in any other way except by aid from Americans.

Let us cast this isolationist, chauvinist poison from our minds before we corrode our hearts and arouse suspicions of our motives in the minds of the decent peoples of the world. Let us cooperate wholeheartedly with the other nations of the world to agree to use atomic energy only for peaceful purposes and to set up an inspection system to enforce such agreement. The United Nations Assembly has voted unanimously to establish an Atomic Energy Commission to draw up such a plan. In the face of the frightfulness of atomic warfare, it is inconceivable to me that any nation will refuse to participate in a program of international cooperation and inspection. Yet, much public discussion, and even more private conversation, is based upon the assumption of such a refusal. We must push forward with all possible speed in order to find out where we stand in the world today so that it is no longer possible for different groups and different nations to base their thinking and their planning upon different hypotheses. I am confident that if we do this, the outcome will be world friendship and cooperation and not atomic war and the destruction of civilization.

Scanning Science—

Nature states that the Toronto Local Committee are assiduously engaged in preliminary work for the meeting of the British Association for the Advancement of Science in 1897. Meetings of the executive committee are held every fortnight. Besides the executive committee, a number of sub-committees are at work, including those on finance, conveyances, publication and printing, rooms for offices, meetings of the association and committees, hotels and lodgings, press, hospitality, reception and for securing cooperation of other institutes, associations and corporations, postal, telegraph and telephone facilities.

—27 March 1896

Obituary

George Dunlap McLaughlin

1887-1945

George D. McLaughlin, director of the B. D. Eisendrath Memorial Laboratory, Racine, Wisconsin, and a leading scientist in the field of leather chemistry, died suddenly on 15 October 1945. His death at the age of 58 ended an unusual career.

He was born at the little town of Retort, Center County, Pennsylvania, in 1887. After finishing high school at Buena Vista, Virginia, young McLaughlin, who, as a boy, had been fascinated by the work of a chemist in a near-by plant, served first as chemist's helper and later, at 19, despite a slender academic background, was given the responsible position of chief chemist of the Leas and McVitty plant in Buena Vista. In 1912 he moved to Benicia, California, where he was chief chemist for Kullman, Salz and Company.

In 1919 McLaughlin dropped industrial work and went to the University of Cincinnati, where he felt he could find opportunity for study and research as a means for seeking answers to many problems that he had found in practical work. At Cincinnati he held a research associateship in physiology. This two-year period of study brought an unexpected reward. The leading tanners of the country had, for several years, maintained a central research laboratory in New York City. They wished to expand this activity and were in need of a director who possessed enthusiasm, scientific curiosity, practical knowledge, and the ability to work with people. McLaughlin accepted the offered position after the tanners had agreed to an unusual proposal from him. The laboratory was to be moved to Cincinnati, was to be associated with the University there, and, when so located, was to deal with fundamental research rather than "plant problems."

A separate laboratory building was designed, built, equipped, and staffed under McLaughlin's direction and was soon producing basic and fundamental scientific findings for both science and industry. Young men were added to the staff from time to time. Many of them later went out into work elsewhere, carrying the benefits of McLaughlin's training and stimulating approach.

Moreover, he held a post in the University—as one of his friends said, that of "dean without portfolio," for his administrative skill and understanding of personnel questions, coupled with his close friendship with the deans of the Engineering and Graduate Schools, Dr. Herman Schneider and Dr. Louis [illegible] More, drew him increasingly into the role of advis[illegible] on university problems. Thus, his influence was wi[illegible] spread in the local community and was extended, wi[illegible] his wife's, pianist and painter, to the artistic a[illegible] intellectual life of the city.

By 1931 administrative duties had pyramided, lea[illegible] ing little time for research work. Again opportuni[illegible] and the chance to create another research group wa[illegible] at hand. The result was the B. D. Eisendrath M[illegible] morial Laboratory at Racine, unique in the tannin[illegible] industry and made possible by his friend, David [illegible] Eisendrath, president of the B. D. Eisendrath Tannin[illegible] Company. More research and further contribution[illegible] to science and industry followed. His last work wa[illegible] as senior author of the recently published America[illegible] Chemical Society Monograph, *The chemistry of leathe[illegible] manufacture,* into which he poured his unusual com[illegible] bination of practical but well-considered experienc[illegible] and keen and painstaking research.

In recognition of his work and contributions he wa[illegible] awarded the honorary degree of Master of Science b[illegible] the University of Cincinnati in 1924. In 1937 he be[illegible] came the first recipient of the Fraser Muir Moffat[illegible] Gold Medal, awarded by the Tanners' Council Re[illegible] search Foundation. He had served as president of the[illegible] American Leather Chemists Association, of the Cincinnati Section of the American Chemical Society, and of the Cincinnati Chapter of Sigma Xi.

Despite his deep and active interest in his studies, his thoughtful mind ranged far beyond his scientific work. Enthusiastic over history, widely read in philosophy, a lover of music and the graphic arts, he was serving as chairman of the Racine Art Association at the time of his death. A special fund, set up in his name by contributions from friends and admirers, has been established to further the work of the Wustum Museum of Fine Arts in Racine.

Such men as George McLaughlin, beginning as apprentice chemist and rising through his ability, probity, and energy to leadership in his profession, reaffirm in practice the very best traditions of the American democracy to which he was so devoted.

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Technical Papers

Some Physical and Biologic Properties of Subtilin and Other Antibiotics[1]

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Subtilin, an antibiotic obtained from *Bacillus subtilis* by Jansen and Hirschmann in 1944 (*4*), was found to be active *in vitro* against *Staphylococcus aureus, Lactobacillus casei, Micrococcus conglomeratus,* and *Streptococcus viridans.* Salle and Jann (*10*) have indicated that it is also active *in vitro* against gram-positive bacteria including *Mycobacterium tuberculosis.* It was reported by them to have a cytotoxic index of about 20. Because of its favorable antibiotic activity we desired to investigate possible modes of action against a variety of organisms. Effects on *Trypanosoma equiperdum, Leishmania donovani, Endamoeba histolytica, Lactobacillus plantarum,* and *Ascaris suis* were studied. In addition, physical behavior was considered in an effort to explain the biologic activity of subtilin and other antibiotics *in vitro* and *in vivo.*

Using the technic of Heilman and Herrell (*3*), subtilin,[2] 0.05 per cent in water or in 85 per cent ethyl alcohol, showed immediate surface-tension-lowering effect. Gramicidin, as noted by Heilman and Herrell (*3*), and gramicidin derivative (formaldehyde treated), prepared by Lewis, *et al.* (*6*), exhibited similar properties. Lysozyme and streptomycin[3] produced only slight effects, while penicillin[4] did not alter surface tension. Fig. 1 summarizes our findings. The Cenco-Du Noüy tensiometer was used.

The hemolytic effect of gramicidin, reported by Heilman and Herrell (*2*), was compared with that of the other antibiotics. Confirming the studies of Lewis, *et al.,* gramicidin derivative proved less hemolytic. Subtilin had no immediate effect on red cells, but after 24 hours at 4° C. hemolysis occurred. Penicillin and streptomycin caused no hemolysis, thus confirming Van Dyke (*11*) with respect to penicillin.

Brief exposure of *T. equiperdum* to subtilin dissolved in 0.45-per cent sodium chloride solution resulted in immediate cytolysis when 1:2,000 dilution was used. Streptomycin and penicillin were not lytic. Survival of trypanosome-infected mice was not prolonged when 80 to 160 mg./kg. amounts of subtilin were given intraperitoneally.

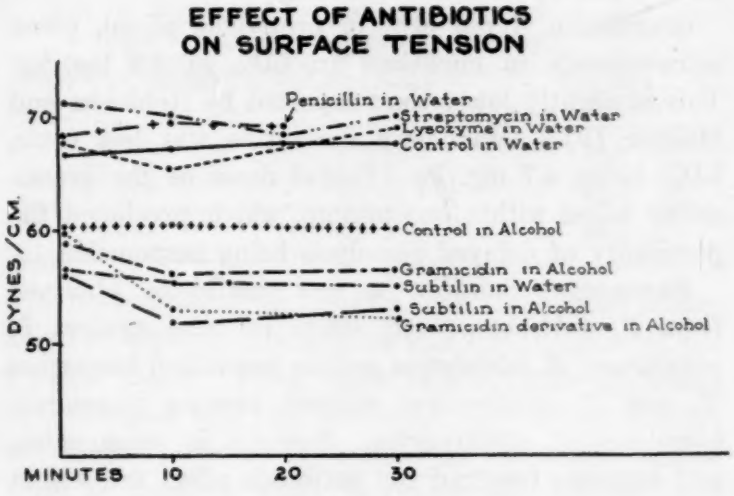

FIG. 1

Using a previously described technic (*7*), subtilin was not active *in vitro* or *in vivo* against *L. donovani.* Penicillin G in 1:1,000 dilution caused cytolysis of leishmania in 6 hours, and in 1:10,000, in 24 hours. *In vivo* it was not active. Neither streptomycin nor lysozyme was effective *in vitro.*

E. histolytica was killed *in vitro* in liquid liver medium (*1*) at 1:400,000 dilution of subtilin, as well as the associated bacterium 't'. In egg slope medium it was active within the range of emetine hydrochloride, and on autoclaving solutions for 10 minutes, subtilin's activity was markedly enhanced. The gramicidins had similar activity in egg slope medium, but were only one-fifth as active as subtilin in liquid liver medium. Streptomycin in 1:2,500 dilution killed the ameba *in vitro.* Penicillin has been reported ineffective (*8*). One monkey (*Macacus rhesus*) was cleared of *E. histolytica* for three weeks after 1.0 gram/kg. total oral doses in 10 days.

Against *L. plantarum* (342y) in liquid medium containing 1 per cent dextrose and 1 per cent Difco yeast extract (pH 6.8), a 1:80,000 dilution of subtilin inhibited growth after 48 hours at 37° C. Cholesterol did not enhance its activity, but para-aminobenzoic

[1] Part of a cooperative study with Dr. Howard D. Lightbody and associates, Western Regional Research Laboratory, U. S. Department of Agriculture, Albany, California, who produced the antibiotics reported (unless otherwise acknowledged); together with Dr. A. J. Salle, Department of Bacteriology, University of California at Los Angeles. Studies in the University were supported, in part, by Eli Lilly and Company, Indianapolis, Indiana, and the Committee on Medical Research, Office of Scientific Research and Development, under contracts with the University of California. Acknowledgment is made to Dr. Benedict E. Abreu and to Mrs. Elsa Zitcer, who performed some of the toxicity tests in mice.

[2] Amounts of antibiotics are expressed on the basis of weight of dry materials, except for penicillin (C.S.C.).

[3] Generously supplied by the Lilly Research Laboratories, Indianapolis, Indiana: streptomycin, 350 units/mg.; penicillin G, 1,650 units/mg.

[4] Sodium salt, prepared by Commercial Solvents Corporation.

acid did. The gramicidins were active at 1:40,000 dilution and streptomycin at 1:10,000.

In vitro tests against *A. suis,* using the technic of Lamson and Brown (*5*), revealed that none of the antibiotics studied was active.

The acute toxicity of subtilin in mice, on intravenous injection of 1 per cent solution, was LD_{50} (60 ± 3 mg./kg.); on subcutaneous injection, the LD_{50} was 670 ± 30 mg./kg.; when given intragastrically, 5.0 grams/kg. killed. One per cent solution instilled into the rabbit's eye was nonirritating.

Gramicidin, 1 per cent in propylene glycol, given intravenously in mice had an LD_{50} of 1.5 mg./kg. This is slightly lower than reported by Robinson and Molitor (*9*). Gramicidin derivative was less toxic, LD_{60} being 4.7 mg./kg. Lethal doses of the gramicidins killed within one minute, which precluded the possibility of delayed hemolysis being responsible.

Summary. Subtilin, a new antibiotic obtained from *B. subtilis,* proved active *in vitro* against *L. plantarum, E. histolytica* and its associated bacterium 't', and *T. equiperdum* without causing immediate hemolysis of erythrocytes. Subtilin is tensioactive, and amounts required for antibiotic effect are within the range of surface tension activity. It was relatively nontoxic for four species of mammals, especially after intragastric administration. Gramicidin is more hemolytic and more toxic than subtilin.

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A Relation Between Size of the Divalent Cation and Solubility of Triple Acetate Salt of Sodium

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The importance of the size of the alkali metal cation to the formation of the triple acetate salt, $NaM^2UO_2(OAc)_9 \cdot 6H_2O$, was first demonstrated by Caley and Baker (*2*) when they proved that potassium, unlike lithium and sodium, formed only a double salt. In their paper, they listed the divalent ions which form triple acetate salts with sodium in a order of decreasing sensitivity toward sodium. Their list is reproduced in Table 1, together with the em-

TABLE 1

Radii of Divalent Cations Which Form Triple Acetate Salts Arranged in Order of Decreasing Sensitivity of Their Respective Reagents Toward Sodium

Cation	Radii in Angstrom Units		
	Ionic	Atomic	
Mg	0.65	1.62	
Ni	0.70	1.24	
Co	0.72	1.26	
Zn	0.74	1.37	
Fe	0.75	...	
Mn	0.80	1.36	
Cu	...	1.28	
Cd	0.97	1.52	
Hg	1.10	1.55	(liquid)

pirical ionic radii of Pauling (*5*) and the atomic radii of Goldschmidt (*3*). It can be seen that the solubility of the triple salt increases with the radii of the ions, whereas it bears no relation to the radii of the atoms.

Caley and Baker did not assign a position to the ferrous acetate reagent because the difficulties involved in handling it made its exact position in the group uncertain. However, the value of the ionic radius of the ferrous ion establishes the position of reagent between those of zinc and manganese.[1]

TABLE 2

Radii of Alkaline Earth Metals Other Than Magnesium

Cation	Radii in Angstrom Units	
	Ionic	Atomic
Be	0.31	1.05
Ca	0.99	2.21
Sr	1.13	....
Ba	1.35	....

Likewise, if the assumption is correct that the solubility varies with the ionic radius, one should be able to assign a value to the radius of the cupric ion because the sensitivity of its reagent is known. Unfortunately, the limits are very wide, so additional information must be sought. The radius of the cuprous ion is known (0.96 A.—Pauling), as is the magnitude of the change in the radius resulting from the loss of an electron by the ferrous ion (0.15 A.). Although the conditions are not exactly the same for the ferrous ion and the cuprous ion, they are sufficiently similar to enable one to guess that the radius of the cupric ion is approximately 0.81 A.

From Table 2 one might predict that the radii of the divalent ions of the alkaline earth group do not

[1] In a private communication, Dr. Caley stated that this position is consistent with his observations.

all into the range of those of the heavy metals and therefore are not likely to form triple acetate salts. One must admit, however, that other factors, such as the solubility of an individual acetate or the solubility of a double salt, together with the coordination number of the ion, may limit the possibility of the formation of a triple salt. It is interesting to note, therefore, that although a triple acetate has been reported for beryllium (*1*), the findings are open to question according to the work of another investigator (*4*). To date, no triple acetate has been reported for calcium, although very early work (*6*) reported two varieties of double salt, one of which might have been a triple salt. No triple salts of strontium or barium are known. Hence, it appears that the size of the ionic radius of a divalent ion not only affects the solubility of the triple acetate salt within the group listed in Table 1 but also provides a means of predicting whether or not any divalent cation is likely to form a triple acetate salt.

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The Mechanism of the Therapeutic Effect of Iodine on the Thyroid Gland

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It is now a well-established fact that in cases of toxic goiters the iodine produces an effect which, clinically, shows relief of the symptoms and, biochemically, decrease of the circulating thyroid hormone and an increase in the gland of total iodine, both free and organically bound. Histologically, this effect is manifested by the deposit of the colloid inside the follicles. These facts are generally interpreted as a blockage of the release of the secretion by iodine, but its mechanism is still not very well understood.

The theory of a mechanical blockage, supported by several authors (*5, 6*), can be hardly maintained in view of the modern concepts of enzymatic chemistry and histophysiology of the thyroid gland.

Salter and Lerman (*7*), as the result of a study of enzymatic synthesis carried out with proteases as catalysts, suggested that the therapeutic effect of iodine is due to the mass-law phenomenon, which acts by "forcing" the reaction in the direction of a synthesis and, in this way, inducing the colloid formation and storage.

In 1941 one of us (*1*) demonstrated that the colloid of rat thyroids, extracted from a single follicle, has a definite proteolytic activity, and established a correlation between this activity and the function of the thyroid gland. From these results, later confirmed by Dziemian (*3*), the conclusion was drawn that in the reabsorption of the colloid an enzymatic mechanism is involved which is responsible for the proteolysis of thyreoglobulin. It also was found that iodine, after a certain time, inhibits this proteolytic activity.

TABLE 1

Proteolytic Activity of Toxic Goiters Before and After Treatment *in Vitro* With Iodine

Blank Mg. of tyrosine and tryptophane set free	Iodinized extract Mg. of tyrosine and tryptophane set free	Per cent inhibition
0.116	0.031	73.3
0.164	0.035	77.1
0.094	0.042	55.3
0.225	0.105	53.4
0.092	0.011	88.5

Recently we found (*2*) in human thyreotoxicosis that the proteolytic activity of the total gland, as measured by the amount of tryptophane and tyrosine set free, is probably also decreased through the action of iodine administered in therapeutic doses. These results and those of Henrriott (*4*) on the inhibition of pepsin activity by iodization *in vitro,* led us to suppose that in the case of iodine treatment the clinical effect is due to an inhibition of the proteolytic enzyme system.

In order to test this assumption, glycerol extracts of human thyroid gland (toxic goiters) were iodinized *in vitro* with a final concentration (0.05 M) of iodine, and the proteolytic activity was determined by the amount of tyrosine and tryptophane set free after a 4-hour incubation at 37° C. with edestin as substrate. The details of this method were described in our previous paper (*2*). Here we wish only to add that the glycerol extracts, after iodinization, were dyalized for 24–48 hours at 3° C. Also, the blank (*i.e.* the same extract, but without iodine) was treated in the same way.

Certain of the results of this experiment are given in Table 1, from which the conclusion may be drawn that, under these conditions, there is 53.4 to 88.5 per cent inhibition of the proteolytic activity of the thyroid gland. It is interesting to point out that this

inhibition is due to free iodine, as control experiments with potassium iodide (which serves as a solvent medium for the iodine in our iodinization experiments) show no inhibiting effect whatever. The same may be said about the thiourea, which obviously acts through a different mechanism.

From our experiments we conclude that the therapeutic action of iodine on the thyroid gland is due to the inhibition of the proteolytic enzyme system, probably responsible for the release of the follicular colloid.

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Brain Involvement as a Possible Cause of Relapse After Treatment in Spirochetal Relapsing Fever

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Schuhardt and O'Bryan (*1*) have reported that doses of 40,000+ units (per kilogram body weight) of penicillin sodium, when injected intraperitoneally over a period of 72 hours beginning at onset of the first attack, will cure blood-stream involvement and prevent most brain involvements in *Ornithodorus turicata*-transmitted relapsing fever of the white rat. Equivalent intraperitoneal doses given at later stages of the infection failed to cure brain involvement. Subsequently, these workers (*2, 3*) reported cure of brain involvement by the intracranial injection of 1,000 units of penicillin. These observations provide a means of testing the theory that relapse after treatment in spirochetal relapsing fever can be a consequence of the persistence of spirochetes in the central nervous system of the treated animals.

This tendency to relapse after treatment is a fundamental problem, not only in the case of spirochetal relapsing fever but also in that of spirochetal diseases generally. Also, the problem of therapy in neurosyphilis conceivably is related to the problems here involved. Furthermore, we believe that much of the confusion in the literature relative to the use of relapsing-fever-spirochete infected animals in testing spirocheticidal agents stems from the irregular tendency of these animals to relapse after treatment.

In our experimental work 53 rats were infected by the intraperitoneal injection into each of 0.01± ml. of onset positive heart blood from tick (*O. turicata*) infected rats. The infection status of these rats, both before and after treatment, was followed by uniform (0.01 ml. of a 1:20 dil.), daily, dark-field examination of tail blood. Penicillin therapy was begun in the test animals on the second or third day of dark-field positivity which, in each case, was the fourth or fifth day of the infection.

Twenty-five of the rats were anesthetized with 3–4 mg. of nembutal per 100 grams body weight, and each received 1,000 units of penicillin in a single intracranial injection (0.05 ml. of a 20,000 units/ml. solution in phosphate buffer pH 7.0). Although many of these rats showed severe convulsive reactions, only 2 died as a result of this injection. The 23 surviving rats received 1 to 14 intraperitoneal injections of penicillin at three-hour intervals, resulting in doses ranging from 4,400 to 50,900 units/kg. body weight.

Nineteen rats received no intracranial penicillin, but received 1 to 16 intraperitoneal injections at intervals of three hours, resulting in penicillin doses of from 10,100 to 52,500 units/kg. body weight. These rats served as controls for comparing the effect of combined (intracranial and intraperitoneal) therapy with intraperitoneal therapy alone. Nine additional rats served as untreated controls. Eight of these relapsed one or more times during the experiment, and all 9 were brain-blood-passage positive at the end of 31 days.

Too few rats were included in the group receiving 30,000 to 40,000 units/kg. body weight intraperitoneally to draw final conclusions relative to the mini-

TABLE 1

No. rats	Penicillin therapy			No. showing microscopic relapse	Brain-blood passage results	
	Intracranial	Intraperitoneal				
	Amount	No. inj.	Units/kg.		No. passed	No. pos.
13	1,000 units	1 to 10	4,400–22,800	12	1	1
14	None	1 to 10	10,100–35,900	12	2	2
6	1,000 units	4	41,000–50,500	Not examined	6	3
4	1,000 units	10 to 14	42,400–50,900	0	4	0
5	None	10 to 16	47,600–52,500	3	2	2
9	None	None		8	9	9

m curative intraperitoneal dose of penicillin. wever, all 27 rats which received less than 40,000 its/kg. intraperitoneally either relapsed microscopi- ly or were brain-blood-passage positive regardless whether or not they received intracranial therapy. we can accept the growing evidence that 1,000 its of penicillin is adequate to sterilize the brain an infected rat, the relapses and positive brain ssages in the 13 animals in this group, which re- ved intracranial penicillin, were the consequences inadequate intraperitoneal therapy to cure the od stream and/or visceral tissues.

Fifteen rats received intraperitoneal penicillin total- g from 41,000 to 52,500 units/kg. body weight. n of these rats each received an additional 1,000 its intracranially. These 10 rats were subdivided o a group of 6 which received more than 40,000 its/kg. in 4 intraperitoneal injections and a group 4 which received equivalent total amounts of peni- lin in 10 to 14 intraperitoneal injections. The 5 maining rats in this group, which received no intra- anial penicillin, received from 47,600 to 52,500 its/kg. in 10 to 16 intraperitoneal injections.

The 6 rats which received only 4 intraperitoneal jections were not examined microscopically for re- pses. Brains were passed from these animals within days after treatment, and 3 were found to be posi- ve. Since each brain passage includes varying mounts of adhering blood, we are inclined to inter- ret these 3 positive passages as instances of blood ssage resulting from the short duration of the traperitoneal therapy.

The 4 rats which received combined therapy and e more than 40,000 units/kg. intraperitoneally in 0 to 14 injections were examined microscopically for 1 days, during which time none relapsed. Brain passages from these 4 animals were all negative. Thus, it is again demonstrated that adequate combined intracranial and intraperitoneal penicillin therapy will cure both brain and blood-stream involvement in experimental relapsing fever.

The 5 rats which received no intracranial penicillin but received 47,600 to 52,500 units/kg. intraperi- toneally in 10 to 16 injections were examined micro- scopically each day until they relapsed, or for 31 days. Three of these rats relapsed in 11 to 16 days. The two which did not relapse in 31 days were found to be brain passage positive and can be assumed to have been potentially capable of relapsing had the examination period been extended. This irregular relapse tendency undoubtedly has been the cause of much confusion in chemotherapeutic studies in experi- mental relapsing fever. We believe that the use of intracranial or intracisternal penicillin will serve as a distinct aid in future testing for the blood-visceral efficacy of other spirocheticidal agents in rats.

The results of these experiments prove that relapse after intraperitoneal treatment in experimental relaps- ing fever can result from spirochetes re-entering the blood after persistence in the central nervous system during the course of treatment. Undoubtedly some of the numerous instances of relapse after intravenous arsenic therapy in human relapsing fever can be ex- plained similarly.

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The Ambiguity of International Antitoxic Units[1]

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The labels on the bottles of commercial polyvalent antitoxin now being used in the prophylaxis and treat- ment of gaseous gangrene are very misleading. For example, "one therapeutic dose" of a certain brand of such antitoxin is stated to contain:

10,000 units *B. perfringens* antitoxin
10,000 units Vibrion septique antitoxin
3,000 units *B. histolyticus* antitoxin
1,500 units *B. oedematiens* antitoxin
1,500 units *B. Sordellii* antitoxin

One would naturally suppose the units of these five antitoxins to be of equal protective power; such a serum would seem to be very strong in protective action against *B. perfringens* and "Vibrion septique" (*B. septicus*), less than a third as strong against *B. histolyticus,* and only about one-seventh as strong against *"B. oedematiens"* (*B. Novyi*) and *B. Sordellii.*

As a matter of fact, no two of the international units for these antitoxins have the same protective power in terms of minimal lethal doses of their respec- tive toxins in mice. The papers of Bengston, Stew- art, and Ipsen (*2, 3, 4*), who established the interna- tional standards for these antitoxins under the auspices of the Permanent Committee of Standardization of the Health Organization of the League of Nations, show the approximate values indicated in Table 1.

It is, of course, impossible to establish and main- tain an exact relationship between the number of

[1] The work in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University. Dr. Frank L. Meleney, of the Subcommittee on Surgical Infections, was the responsible investigator.

minimal lethal doses of different lots of toxin and a "unit" of antitoxin, owing to the varying ratios of active toxin and inactive toxoid occurring in different toxic filtrates. It is well known that both toxins and toxoids combine with antitoxins. The original standard units of diphtheria, tetanus, and botulinus antitoxins were based upon test doses of more or less stabilized toxins measured in minimal lethal doses for guinea pigs of standard weights from which an initial

TABLE 1

Antitoxin	Approximate number of mouse M.L.D.'s neutralized by 1 unit	Units in "therapeutic dose"	Approximate number of mouse M.L.D.'s of toxin neutralized
B. perfringens	50 to 70	10,000	500,000 to 700,000
B. septicus (Vibrion septique)	40 to 64	10,000	400,000 to 640,000
B. histolyticus	45	3,000	135,000
B. Novyi (*B. oedematiens*)	5,000	1,500	7,500,000
B. Sordellii	1,900 to 3,800	1,500	2,850,000 to 5,700,000

provisional and reasonably stable unit of serum could be defined, but it was always necessary to titrate each lot of toxin against the standard antitoxic unit when ascertaining the titer of new lots of antitoxins. And the number of minimal lethal doses in the test doses from different lots of toxin was found to vary considerably. In fact, the same antitoxin tested against different toxins equated to the same standard unit sometimes gave different values. The same principle holds for the gas-gangrene antitoxins, yet there is, in all cases, an approximate relationship between unitage and protective power. It thus appears in the above "therapeutic dose" of polyvalent gas-gangrene antitoxin that while the number of units of *B. perfringens* and *B. septicus* antitoxin is large, their protective power is greatly exceeded by a much smaller number of units of *B. Novyi* and *B. Sordellii* antitoxin.

There has been considerable discussion as to the most desirable composition of polyvalent gas-gangrene serums. Some manufacturers, starting some years ago with a mixture similar to the above, in some cases including 1,500 units of tetanus antitoxin, subsequently eliminated all but the antitoxins for *B. perfringens* and *B. septicus* on the ground that these two were the most common causative agents in gaseous gangrene. Tetanus antitoxin was to be given prophylactically in a separate dose. But owing to the increased number of cases of infection with *B. No* in the military campaign in the Middle East (*6*), rec practice has been to include *B. Novyi* antitoxin well, omitting the antitoxins for *B. histolyticus* a *B. Sordellii* on the ground of relative infrequen I favor the inclusion of all five in approximat equal protective ratios, because experience shows th all the above anaerobic bacilli give rise to serio wound infections, and it is impossible for a bacteri logical examination to determine the significant sp cies present in a given case in time to decide whi monovalent serum should be used.

It is really unfortunate that the standardization antitoxin serums was not developed so that an a proximately equal protective power was always d noted by the term "antitoxin unit." Even the mu older units of diphtheria, tetanus, and botulinus ant toxins differ from each other and from the above relative protective power. The diphtheria unit w originally defined as that amount of serum whi would protect a 250-gram guinea pig for 96 hou against a test dose (L_+) of diphtheria toxin of 1 minimal lethal doses (*5*), while the tetanus antitox unit was defined in the United States as 10 times th amount of serum which would protect a 350-gra guinea pig against a test dose of 100 minimal leth doses (*7*), and botulinus antitoxin was standardize like tetanus antitoxin except that guinea pigs weighin 250 grams were used (*1*).

The gas-gangrene antitoxin units defined in term of minimal lethal doses of toxin for mice are all di ferent from those of diphtheria, tetanus, and botulis in terms of minimal lethal doses of these toxins fo guinea pigs. Although the values overlap betwee *B. perfringens* and *B. septicus* antitoxins and betwee *B. tetani* and *B. botulinus* antitoxins, the discrepancies in the list as a whole and the over-all range are con spicuous.

Perhaps a new international committee on stand ardization might consider redefining antitoxic units i terms of approximately equal protective power i order to simplify as far as possible our now confused conceptions.

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U. S. News and Notes

Max A. Lauffer, associate professor of physics at the University of Pittsburgh, will receive at Atlantic City on 12 April the $1,000 Eli Lilly and Company Award in Biological Chemistry for his work on viruses. Dr. Lauffer will speak on "Contributions of Virus Research to Chemistry and Physics" to the American Chemical Society's Division of Biological Chemistry.

J. W. T. Youngs, of Purdue University, has been made associate professor of mathematics at Indiana University.

Dr. Homer C. Thompson, head of the Department of Vegetable Crops, Cornell University, addressed the Plant Institute of the Ohio State University on 25 February. Dr. Thompson, who received the three collegiate degrees from Ohio State, spoke on "The Importance of Micronutrients in Vegetable Production" in participating in the Twenty-fifth Anniversary Program of the Plant Institute.

Announcements

The Ella Sachs Plotz Foundation for the advancement of scientific investigation made 23 grants-in-aid during 1945, the twenty-second year of its existence. In the past, 531 grants have been distributed to scientists throughout the world. The current list follows:

Dr. Clemens E. Benda, Wrentham State School, Wrentham, Massachusetts: the development of the anterior pituitary lobe from birth to adolescence and the main patterns of pathology in various disorders.

Dr. H. Bernkopf, The Hebrew University, Jerusalem, Palestine: work on influence of rabies virus on the metabolism of brain tissue of chicken embryos and mice.

Dr. T. T. Chen, University of California, Los Angeles: publication of two-colored plates illustrating cytological studies of malarial parasites.

Dr. S. J. Crowe, Johns Hopkins University School of Medicine, Baltimore: continuation of work on chronic occlusion of the Eustachian tube by hyperplastic lymphoid tissue in the region of its nasopharyngeal orifice.

Prof. M. S. Dunn, University of California, Los Angeles: continuation of investigation of peptides.

Dr. Anna Goldfeder, New York University College of Medicine, New York City: continuation of studies on the relation between radiation effects and cell viability as indicated by induced resistance to transplanted tumors.

Dr. A. Sydney Harris, Western Reserve University School of Medicine, Cleveland, Ohio: a study of the effects of anoxia on the heart.

Dr. H. Heller, University of Bristol, Bristol, England: investigation of the renal function of newborn mammals in comparison with adult.

Dr. Harold Holck, University of Nebraska, Lincoln: work on the relation of sex to drug action.

Dr. W. Henry Hollinshead, Duke University School of Medicine, Durham, North Carolina: investigation into the functions of the abdominal chemoreceptors of the mouse and rat.

Dr. George W. Holmes, Massachusetts General Hospital, Boston: publication of material on the effect of cathode rays on the human skin.

Dr. V. Korenchevsky, Oxford, England: research on aging.

Dr. Otto Krayer, Harvard Medical School, Boston: analysis of certain phenomena of nerve and muscle related to the "veratrine response" of these tissues, and work pertaining to the distribution and activity of cholinesterase, by Drs. George H. Acheson and Ralph W. Brauer.

Prof. J. V. Luco, Santiago de Chile, South America: research in the field of neurophysiology.

Prof. Carl Neuberg, New York University, New York City: continuation of physiological investigations of the osones.

Dr. William T. Salter, Yale University School of Medicine, New Haven: study of the action of cardiac glycosides and other cardiotrophic substances upon fatigued heart muscle.

Dr. F. O. Therman, Nobel Institute for Neurophysiology, Karolinska Institutet, Stockholm, Sweden: continuation of neurophysiological research.

Thorndike Memorial Laboratory, Boston City Hospital, Boston (Prof. George R. Minot, director): in recognition of Dr. Francis W. Peabody's services to the Foundation.

Dr. Edward J. Van Liere, West Virginia University School of Medicine, Morgantown: continuation of research on the effect of anoxia and asphyxia on animals, to include intestinal absorption and motility.

Dr. William J. van Wagtendonk, Oregon State College, Corvallis: investigation of the enzyme systems responsible for the derangement of the purine metabolism during the deficiency of the antistiffness factor.

Dr. E. Wertheimer, The Hebrew University, Jerusalem, Palestine: investigation of *in vitro* synthesis of glycogen from glucose by liver and diaphragms of diabetic rats.

Prof. Richard W. Whitehead, University of Colorado School of Medicine, Denver: continuation of investigations into "diffusion respiration."

Prof. Bernhard Zondek, Rothschild Hadassah University Hospital, Jerusalem, Palestine: continuation of investigations dealing with the impairment and stimulation of the functions of the pituitary gland and especially of the gonadotropic hormones of the anterior pituitary lobe.

Applications for grants to be held during the year 1946–47 must be in the hands of the Executive Com-

mittee before 15 April 1946. There are no formal application blanks, but letters asking for aid must state definitely the qualifications of the investigator, an accurate description of the research, the size of the grant requested, and the specific use of the money to be expended. In their requests for aid applicants should state whether or not they have approached other foundations for financial assistance and what other sources of support are relied on for research. It is highly desirable to include letters of recommendation from the directors of the departments in which the work is to be done. Applications should be sent to Dr. Joseph C. Aub, Massachusetts General Hospital, Boston 14, Massachusetts.

The Joint Army-Navy-NDRC Tropical Deterioration Information Center, which operated under contract with the George Washington University during the war, has been transferred to the National Research Council under a contract between the Navy Department and the National Academy of Sciences. The project has been renamed The Prevention of Deterioration Center. The functions of this project are: (1) to maintain and operate a coordination center; (2) to maintain personal contact with all work on the prevention of deterioration; (3) to act in a consulting and advisory capacity on deterioration; and (4) to conduct certain studies in this field at the request of the Armed Forces.

The 125th anniversary celebration of the Philadelphia College of Pharmacy and Science was held on 22 February in Philadelphia. At ceremonies in the college auditorium representatives of nearby universities and colleges, learned organizations, and professional societies heard a review of the influence of the founding Quakers on Philadelphia's institutions, presented by Dr. George Urdang, director of the American Institute for the History of Pharmacy, Madison, Wisconsin.

The National Registry of Rare Chemicals, Armour Research Foundation, 35 West 33rd Street, Chicago 16, Illinois, lists their new needs as follows: thianaphthene; coniferyl alcohol; uridylic acid, d- or l-fenchone; ornithin; azulene; diphenyl phosphate; 3,4-dihydroxy pyridine; trimethylene diamine; tetramethylene diamine; pentamethylene diamine; humic acid; 2-phenyl cyclohexanol; 1,1-dibrompropane; strophanthidin; digoxigenin; digitoxigenin; periplogenin; cyclobutane; pyrithiamine; 1-rhamno ascorbic acid; d-arabo ascorbic acid; α- or β-angelica lactone; tributyl boron. Please communicate regarding these directly with the Registry at the address given above.

Meetings

Three lectures on Electrical Communication—Roots and Branches will be given by Dr. J. Ow Perrine, assistant vice-president, American Telepho and Telegraph Company, in the auditorium of t Wagner Free Institute of Science, Montgomery Av nue and 17th Street, Philadelphia. The subjects w be: "Entangling Alliances of Electricity," 12 Apri "Waves, Carriers of Power and Information," April; "Radar and Microwaves," 26 April. Lectur are to begin at 8:00 P.M.; admission is free.

The newly formed Eastern Association of Electr encephalographers will meet at the Graduate Club o the Institute of Living, Hartford, Connecticut, at 1:0 P.M., Friday, 12 April 1946, at which time a draft o the constitution and bylaws will be presented by th Organization and Program Committee. Military ex perience in electroencephalography will be discusse by Dr. Milton H. Kibbe, who will speak of the Army and Dr. Charles B. Henry, who will report on Nav data. This is the second meeting of the group.

Elections

Officers of the Washington Academy of Sciences for 1946 are: Hugh L. Dryden, president; F. G. Brickwedde, secretary; Howard S. Rappleye, treasurer. Vice-presidents representing the Affiliated Societies are: Francis M. Defandorf, Philosophical Society of Washington; T. Dale Stewart, Anthropological Society of Washington; Frank Thone, Biological Society of Washington; Leo A. Shinn, Chemical Society of Washington; Carl F. W. Muesebeck, Entomological Society of Washington; Alexander Wetmore, National Geographic Society; Louis W. Currier, Geological Society of Washington; Frederick O. Coe, Medical Society of the District of Columbia; Gilbert Grosvenor, Columbia Historical Society; L. Edwin Yocum, Botanical Society of Washington; William A. Dayton, Washington Section of the Society of American Foresters; Frank B. Scheetz, Washington Society of Engineers; Francis B. Silsbee, Washington Section of the American Institute of Electrical Engineers; Walter Ramberg, Washington Section of the American Society of Mechanical Engineers; Mario Mollari, Helminthological Society of Washington; Chester W. Emmons, Washington Branch of the Society of American Bacteriologists; Clement L. Garner, Washington Post of the Society of American Military Engineers; Herbert Grove Dorsey, Washington Section of the Institute of Radio Engineers; Owen B. French, Washington Section of the American Society of Civil Engineers. The elected members of the Board of Managers for a term of three years are Max A. McCall and Waldo L. Schmitt.

International News

Dr. Ross G. Harrison, Sterling professor of biology, emeritus, Yale University, and chairman of the National Research Council, has been elected foreign associate of the Académie de Médecine, Paris.

Dr. Bernard E. Read returned in March to Shanghai to take up his duties as the newly appointed director of the Henry Lester Institute of Medical Research, 18 Avenue Road, Shanghai. In spite of the war, the library of this Institute is intact but now lacking American journals published since December 1941. The Institute would appreciate gifts of these journals or of any other medical publications made during the war years.

Dr. E. A. Kreiken, one of the Netherlands astronomers on Java, has written recently to Dr. Bart J. Bok giving further details about the suffering of Indonesia. A recent issue of *Science* (1945, **102**, 642) announced that Dr. Aernout de Sitter, director of the Bosscha Observatory at Lembang, and Dr. Chr. W. Martin had died in Japanese prison camps, and that Mr. J. Utterdijk was lost in the sinking of a transport. This is confirmed by Dr. Kreiken, who adds that Dr. G. V. Simonow and Mr. Witlox, both of the Bosscha Observatory, have also died in captivity. The only two survivors of the seven Dutch astronomers on Java are the former director of the Bosscha Observatory, Dr. J. G. E. G. Voûte, and Dr. Kreiken. Dr. Kreiken states that the Bosscha Observatory lies beyond the narrow, so-called "protected" zone around Bandoeng. It has been impossible for him to obtain information about its condition, but he is not hopeful. Dr. Kreiken's own library was totally destroyed when his house in Soerabaja was burned.

Dr. H. L. Booij, Laboratory of Medical Chemistry, Leyden (Willem Warnaarlaan 9, Sassenheim, Nederland), is greatly interested in all papers concerning applications of physical chemistry in biology and medicine. He has available some reprints of his papers for exchange.

Dr. Ferdinand Schoofs, professor of pharmacy at the School of Pharmacy, University of Liège, Belgium, who spent some time at Yale in 1927, writes to Clifford S. Leonard, of the University of Vermont, as follows:

> The University of Liège remained open all the time of the war, but our laboratories were working in very bad conditions: want of coal, of gas, of light (blackout), of chemicals, and even of distilled water. The students had to bring with them every day a liter of distilled water bought at a high price in the town.
>
> During the bombardment by the allied forces (accepted with the hope of approaching liberation) and later on during the period of robots (V-1 and V-2) thrown by the Germans, we passed several dangerous hours in the shelters. During the months of December 1944 and January–February 1945 I was living and sleeping in the cellar of my home; I received there several students for their examinations. But this dangerous period is now over and we try to forget it; but what we shall never forget are the cruelties of the Teutons.
>
> We are thankful to the allied forces and especially to the Americans, our liberators. Indeed the Americans delivered Liège in September 1944. On this occasion I met here several American professors, for instance Col. Gates of Ann Arbor. I received several times at my home a young and sympathetic assistant professor, Capt. Gordon of Columbia University; he kindly accepted my request that he lecture to my students concerning research on the estimation of alcohol in the blood.
>
> I have been very busy the last years, but now I attain the age limit (70 years); from the beginning of 1946 I am emeritus, legally obliged to rest, but feeling myself still healthy, I shall try to keep on working as long as possible, but no more doing any compulsory work. . . .

Dr. Pitirim A. Sorokin, professor of sociology at Harvard University, has been elected a foreign member of the Royal Academy of Science of Belgium in the class of the political and moral sciences. The honor was granted at a recent meeting. Dr. Sorokin is a native of Russia, where he was a member of the faculty of the University of St. Petersburg, and has been at Harvard since 1930.

Prof. Dr. M. Minnaert, director of the Observatory, Utrecht, Holland, in a letter dated 26 November 1945 to Dr. A. H. Rosenthal, of the Scophony Corporation of America, tells of his being in a hostage camp near s'Hertogenbosch from 1942 to 1944 and of the difficulties encountered in obtaining food during the winter of 1944–45. In March 1945, the Germans invaded the observatory, removing everything from the workshop and emptying nearly all of the buildings. They did not take away instruments or books, nor did they have time to destroy the machines. At present there are three times as many students as normally, but there is a lack of books and instruments; these cannot be purchased abroad because Holland cannot make available any foreign exchange for this purpose. Just before the start of the war the *Photometrical atlas of the solar spectrum* was published. Further, Dr. Houtgast, working on the Fraunhofer lines, has shown that the

displacement is noncoherent. Mr. H. C. Van de Hulst studied the light-scattering on small globules of some wave lengths extension, while Dr. Minnaert has executed the detail photometry of the moon according to the reciprocity law.

The 112th annual meeting of AAAS has come to a close. The meeting was held under great difficulties in the overcrowded city of St. Louis, but some 2,300 people were finally registered, and attendance at at least one of the evening lectures approximated 3,500.

The official business of the Association was finished at a meeting of the Council called for 4:00 P.M. on Friday, 29 March. Dr. J. B. Conant was in the chair, and approximately 35 Council members were present. Several reports were received from the Executive Committee, and the usual last-minute resolutions were introduced. It was announced that the next meeting is to be held in December at Boston.

The affair contained one item of more than general interest, because at the request of Dr. Arthur Compton, Dr. Conant outlined the new plan for international control of atomic energy which had been announced to the press the night before by the State Department through Secretary Byrnes. The report proposes a new method of energy control through the production of nonexplosive or denatured materials which would be the output of atomic energy plants in the various countries. At one stage in the process of manufacture, according to President Conant, the materials would be dangerously explosive, but it was felt that these materials could not be surreptitiously stored or diverted to the manufacture of high explosives without knowledge of the controlling authority. The basis of the new plan seems to hinge on the adequacy of the denatured materials which are to be the output of the plants. The denatured materials are practically irreversible into dangerous elements because complicated manufacturing plants and an enormous personnel would be required to accomplish this end.

The entire issue of *Science* for 26 April will be devoted to summarizing the scientific papers and reporting the business accomplished at the St. Louis meeting.

The International Council of Scientific Unions will meet in general assembly in London on 22–24 July 1946. Meanwhile its Executive Committee has held a meeting in London attended by representatives of most of the International Unions adhering to the Council. In welcoming the Committee at its opening session Dr. A. V. Hill, foreign secretary of the Royal Society, pointed out that science in its own interest must remain an international concern and that the future of civilization itself depends upon the c cooperation of scientific men throughout the world

The heavy toll of recent years on those promin in the field of international science was revealed the list of members of the Committee who had d since its last meeting: Il Marchese Marconi and Ba Joji Sakurai, vice-presidents; Sir Arthur Eddingt president of the International Astronomical Uni Prof. Nicola Parravano, president of the Inter tional Union of Chemistry; Sir Albert Seward, pr dent of the International Union of Biology; Philippson, general secretary of the Internatio Union of Physics; and General Bourgeois, form vice-president, representing the International Uni of Geography.

The President of the Council, Prof. C. Fabry, w has since died, had been compelled to resign on a count of ill health, and Dr. H. R. Kruyt was elect vice-president in his place.

The Entomological Society of British Columbia he its Forty-fifth Annual Meeting at Lytton, B. C., on February. The following officers were elected f 1946: A. W. Finlay, New Westminster, honora president; G. R. Hopping, Vernon, president; M. Hatch, University of Washington, Seattle, vice-pres dent (Coast); J. D. Gregson, Kamloops, vice-pres dent (Interior); H. B. Leech, Vernon, secretary treasurer; W. G. Mathers, Vernon, auditor; and H Andison, Vernon; G. P. Holland, Kamloops; J. R. J L. Jones, Cobble Hill; J. Marshall, Summerland; an G. T. Mockridge, Cloverdale, advisory board.

Oxford University has accepted a collection of book on ethnology from the library of the late Dr. R. R Marett, and also a grant of 1,200 pounds from the British Empire Cancer Campaign for chemical researches in the Dyson Perrins Laboratory relating to carcinogenic hydrocarbons, oestrogenic agents, and a differential growth inhibitor, 500 pounds of the grant to be earmarked for the provision of a special apparatus, and the remainder for the provision of fees and laboratory expenses for two research assistants.

Gen. Georges Perrier, 74, died at his home in Paris in February 1946. For many years Gen. Perrier was General Secretary of the Association of Geodesy of the International Union of Geodesy and Geophysics. This work is now being carried on at the former address, 19 Rue Auber, Paris 9e, by P. Tardi, "Secrétaire Adjoint." Gen. Perrier was a member of the French Academy of Sciences. In the early years of the present century he was the leader of geodetic expeditions in South America, North Africa, Albania, and Syria.

In the Laboratory

Vibrating Muller for the Preparation of spersions of Fine Pigments Electron Microscopy [1]

HAROLD C. O'BRIEN, JR.
St. Joseph Lead Company, Monaca, Pennsylvania

n the preparation of fine pigments for examination the electron microscope it is often difficult to break rt the smaller aggregates of the material. Where is desired to resolve the ultimate particles in the rograph, a considerable amount of work must be rted upon the pigment.

A small portion of pigment, oil, and plastic are gen- lly placed upon a flat glass plate, and a hand ller is used to press and grind and thus disperse powder in the matrix. From a solution of the xture a thin film is cast upon water and forms a pport for the included pigment particles (*1*). Some her aspects of the technique involving solvents and wetting of pigments have been described (*2*).

In the mulling of fine-particle pigments such as rbon black the aggregates remain unbroken in the m between the muller and the glass plate.

A new mechanical vibrating muller (Fig. 1), greatly creases the work exerted upon such a pigment mix-

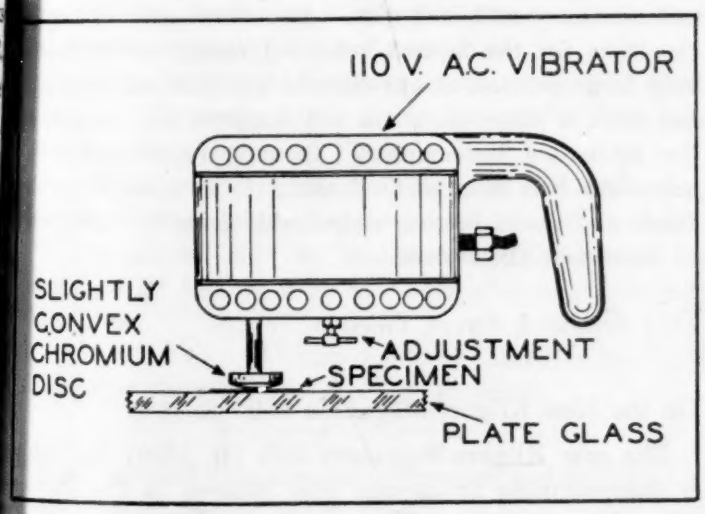

FIG. 1

ture. It consists of a 110-volt A.C. electromagnetic vibrator unit, to which is attached a hardened steel mulling head. The mulling head is very slightly convex so that more perfect contact with the glass plate is obtained. The vibration occurs in an arc with the mulling head shaft as its radius. A handle on the vibrator unit permits hand-mulling concurrent with the vibrating effect.

The use of this device results in greatly increased work upon the pigment through direct contact and through the transfer of energy by vibrations in the matrix. By this method the time and effort required to disperse ultimate particles is substantially decreased.

[1] Acknowledgment is made of the helpful cooperation of the Buhl Foundation Research Project, University of Pittsburgh.

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A Note on the Silencing of Air-stirring Motors

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Air-stirring motors are often viewed with disparagement in the laboratory because of the rather large amount of noise which attends their use. This noise may be traced to four sources: (1) that arising from the turbulent discharge of air from the compressed air lines into tubing connecting with the motor; (2) that due to air rushing through the pipes and the connecting tubing; (3) that inherent in the use of an air motor, *i.e.* bearing noise and the clear tone of audio-frequency which is associated with all turbines; and (4) that resulting from the air rushing out of the small escape ports generally provided in the flat surface on top of the motor. Of these sources, the first and fourth are by far the most important because of both the intensity and the raucous character of the noise arising from them. The devices suggested here have been found very useful in reducing to a very large extent the noise from these two sources. The second and third sources enumerated are of smaller importance, but their contribution to the total noise may be minimized by suitable choice of connective tubing and by judicious oiling.

The noise associated with the discharge of air through a regulating valve from the compressed air lines into the connecting tubing may be reduced greatly if the air flow is controlled not by this valve, but rather by a screw clamp operating on the tubing a few inches from its junction with the air line. If the air is supplied at high pressure, it will probably be found necessary to wire the tubing onto the outlet.

It is thought that the procedure suggested here is effective because the turbulence resulting from the discharge of air under a high-pressure gradient at a sharp corner is eliminated and replaced by laminar flow past the constriction caused by the screw clamp.

The source of sound waves in connection with air discharged through the escape ports is undoubtedly the sharp edges of these ports. If the edges could be rounded and their radius of curvature increased, the noise would probably be reduced greatly. However, such a process is not generally desirable because it effectively requires reconstruction of the motor. The same end may be accomplished by clamping over the motor a small glass funnel, the diameter of which is less than that of the top of the motor but is sufficiently large to permit the funnel to cover the esc ports. The 2½-in. funnels generally available in ch ical laboratories have about the correct diameter that they fit readily over the top of the motor may be held in place by many simple devices. length of the stem is not critical; a very short s seems to be as satisfactory as a long stem and is tainly much less in the way. The device presuma depends in its operation upon minimizing the rela tion oscillations from the escape ports, deadening sound resulting from the oscillations which rema and avoiding further oscillations by discharging air at a smaller rate and in a state more nearly proaching laminar flow. Little or no effect upon efficiency of the motor has been observed.

Letters to the Editor

Safeguarding Science in the NSF

The great interest of scientists in the various bills proposed to support scientific research is amply reflected in the continuing articles in *Science*.

It seems to me that scientists must not lose sight of the fundamental values in such appropriations. They will be valuable directly in proportion as they are valuable for research that is genuinely an effort to seek after the truth. They will become less valuable, and may even become a menace, if they are not protected at the outset so that the unvarnished truth may be sought after and properly published in the scientific journals now available for that purpose.

The history of all federal appropriations for educational research must be carefully scrutinized. There have been instances where funds for such purposes have been deliberately utilized for the production of propaganda to support the program of a given bureau or of a bureaucrat. Such utilization of funds will be condemned by all true scientists wherever they are.

One of the questions seems to be whether or not it is not better to obtain the money first and set up the safeguards afterward, and the rather competent statement is made that there is a certain amount of politics in connection with all funds available, whether it be within the great privately controlled research institutions or whether it be in public-supported research institutions. However, it is my opinion that it is very much better at the outset to put up every available safeguard, even at the risk of losing the appropriation, than it is to attempt to set up these safeguards after the bill or bills are written and entrenched interests established.

One has only to look at the ludicrous findings of the so-called "fact-finding boards" in instances already reported to know that no mathematical genius could ev have found the facts reported in the time that was ava able, coming out with figures that were identical f diverse industries. The layman can only look at t figures and say the fact finders were told what to fi The same sort of figures have been reported in the pr in regard to what constitutes a sustaining diet for o people, and then the figures and results reported in cated that a large portion of the American citizens cou not obtain a sufficient diet. An actual examination the basis for the figures indicated rather clearly that very large portion of our citizens had bad eating habit but such a conclusion did not support the purpose the interested bureaucrats. It must be evident to a scientists that this sort of thing is a waste of publi funds and would become undesirable from the standpoi of scientists themselves.

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On the New Kilgore-Magnuson Bill—S. 1850

The new Kilgore-Magnuson Bill (S. 1850) inevitably is disappointing to anyone who believes in the efficacy of the democratic tradition as accepted in this country. It concentrates power in the hands of too few persons. It does not derive its authority from the "scientific people," great and small. Its great defect is the ease with which it can lead to regimentation. The Administrator provided in this new bill, together with the Board appointed by the President, and the Committees which the Administrator appoints, will be exercising power without the consent of the governed. These are the men and women who actually do the work and who alone are

iciently close to the thinking which underlies scien- advance. No good can come from excluding them m the operation of a scientific organization. This attempts to legislate into existence a profoundly turbing set of administrative devices.

A bill, in order to be acceptable, should contain as a nimum, the following provisions:

A *Constituent Assembly* should be called by the Presi- nt, consisting of representatives, selected by the Presi- nt, from the various forms of institutions of learning, lleges and universities, research institutes, industrial oratories, and government services, lay and military, isting throughout the country.

Recommendations to the President should issue from e deliberations of this Assembly and its appropriate netional committees, including primarily nominations a responsible Board of Directors.

The *Board of Directors* should be appointed by the resident from among the nominees, with the consent d advice of the Senate. This Board should have the wers usually exercised by such Boards in nonprofit embership corporations. The Members of this Board ould devote as much time to the Corporation as may e necessary to its proper functioning and the carrying t of its objectives. The Board should formulate its wn rules of procedure. The Board should be respon- ible at all times to the "Scientific People," represented n an Assembly of Members, which should succeed to the uthority of the Constituent Assembly.

The *functions of the Board should include*:

(1) Carrying out the policies of the Corporation.

(2) Recommending to the President, for his choice, andidates to serve as Administrator. The Administra- or should be responsible to the Board and see to carry- ing out the purposes of the Corporation.

(3) Appointing the Members of the Scientific Com- mittees, on the advice of the Administrator, the Commit- tees appointing their own Chairmen.

(4) Making appropriations and grants and appointing fellows and scholars on the recommendation of the Scien- tific Committees, and in accordance with regulations made by the Board, with the advice of the Scientific Committees.

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The Amino Acid Composition of Proteins and Foods

H. B. Vickery and H. T. Clarke (*Science*, 1945, **102**, 454–456) have questioned the practice of computing the results of amino acid determinations upon a uniform basis as employed in our monograph (*The amino acid composition of proteins and foods.* Springfield, Ill.: C. C. Thomas, 1945).

Four or five years ago, when contemplating the writing of this monograph, the various methods for presenting amino acid data were discussed with a number of work- ers in the protein field. The easiest method, from the authors' point of view, would have been to copy the data in the literature and to present the figures as per cents by weight of substance analyzed in some cases, as amino acid nitrogen in per cent of total nitrogen in others, or as per cent by weight corrected for "moisture" and "ash" in others, etc. A second method would have been to calculate all the data as amino acid nitrogen in per cent of total N. Although this procedure is useful for many purposes, we did not consider it as suitable for a monograph designed primarily for food chemists. A third method, used by Murrill, *et al.* (*J. biol. Chem.*, 1940, **133**, 521), appeared to be most suitable for our objectives.

How intelligible would the first procedure be to the average person whom we believed would use this mono- graph? It would impose a considerable burden on those who wished to compare the results by a number of in- vestigators on the same protein. For example, amino acid values of casein may be given by one investigator as per cent of a sample of commercial casein as analyzed (N = 13.6 per cent); by another, as per cent of the casein corrected for "moisture" and "ash" (N = 14.9 per cent); a third author may hydrolyze a sample of casein and then calculate the quantity of "pure" casein used from a nitrogen determination on the hydrolysate, taking 15.7 as the per cent of nitrogen in casein; etc.

In order to facilitate comparison of analytical data on the same protein by different investigators, we chose an extension of the third method of presentation, namely, calculation of all values to 16 per cent of N. In an attempt to prevent any misunderstanding of our purpose, the original nitrogen values upon which the calculations rested are presented in all except a very few instances, and even in these cases the reasons are explained in the text. Furthermore, repeated examples of how the data in the tables are to be used are given. For instance, on pages x and xi of the Introduction we say: "As all the data in the tables are calculated on the basis of 16 percent of nitrogen, it is only necessary to know the nitrogen content of the protein in order to calculate the data in the tables to give the approximate amino acid composition of the preparation. If the pro- tein contains 18.6 percent of nitrogen on a moisture and ash free basis, then the values in the proper table are multiplied by the factor $\frac{18.6}{16.0} = 1.16$." Other examples are also given here and throughout.

This type of presentation was repeatedly tested before publication by presenting papers containing these cal- culations at protein symposia such as the American Chemical Society at Cleveland, the Cereal Chemists Meet- ing at Minneapolis, the Gibson Island Conferences, and a half dozen other meetings and seminars, as well as by the distribution of much of the data to government agencies and groups interested in food chemistry. At no time was any adverse criticism made of the manner of presentation.

Our monograph was designed primarily to present to the food chemist the widely scattered literature on the methods and results of protein analysis in the most use- ful and practical form. We have sincere doubts concern-

ing the advisability of presenting original data only in this type of monograph. While, if each table had been devised on the basis of a currently accepted value of nitrogen of a pure protein, then it would have been incumbent on the food chemist to make the conversion to the factor he was using for estimating the protein content of the diet. The factor is almost always 6.25. We felt that the protein chemist was equally prepared to perform the reverse calculation. It is quite true that many arguments against this practice may be presented, including those stated many years ago by Kossel, the venerable nature of whose views does not necessarily impart increasing force. The fact remains that "N × 6.25" is not only almost universal, but it is incorporated into the food and feed laws of almost every state in the Union. Almquist (Nutritional Conference, Oregon State College, March 1945) said in this connection: "While it has been shown that this conversion factor differs from 6.25 for certain single foodstuffs, the fact that they are ultimately mixed and accounted for in prepared feeds on the basis of a 6.25 protein factor is ample justification for retaining this factor."

Although we used the N × 6.25 calculation in this monograph, we repeatedly mentioned its limitations and certainly did not advocate it as a general practice in protein chemistry. In fact, in two tables on the amino acid composition of selected plant and animal proteins, prepared by one of us for a recent textbook (Kleiner's *Human biochemistry.* St. Louis: C. V. Mosby, 1945), only the industrially important corn gluten, wheat gluten, soybean proteins, and yeast proteins are calculated to 16.0 per cent of nitrogen. The remaining 14 proteins, being considered purified products, are given on the basis of the best available nitrogen values.

Thus, the so-called calculation error is nullified when the amino acid values are employed in the manner which we designated. However, because the amino acid data could be misconstrued, in spite of the precautions taken, we contemplate presenting the data in the forthcoming revision of this monograph as grams of amino acids per 16 grams of nitrogen in the sample. It is hardly necessary to point out that the actual values given and the mode of calculation to purified proteins or crude foodstuffs remains unchanged.

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Amino Acids in Food Materials

R. J. Block and D. Bolling's recent publication (*The amino acid composition of proteins and foods.* Springfield, Ill.: Charles C. Thomas, 1945) contains 14 tables presenting the amino acid content of a variety of "pure" and mixed proteins from animal and plant sources. The percentage of amino acids in these proteins is uniformly calculated from an assumed 16 per cent of nitrogen in each protein. Of course, the usual procedure was followed of determining the nitrogen in the material to be examined and then multiplying by 6.25 for conversion to protein.

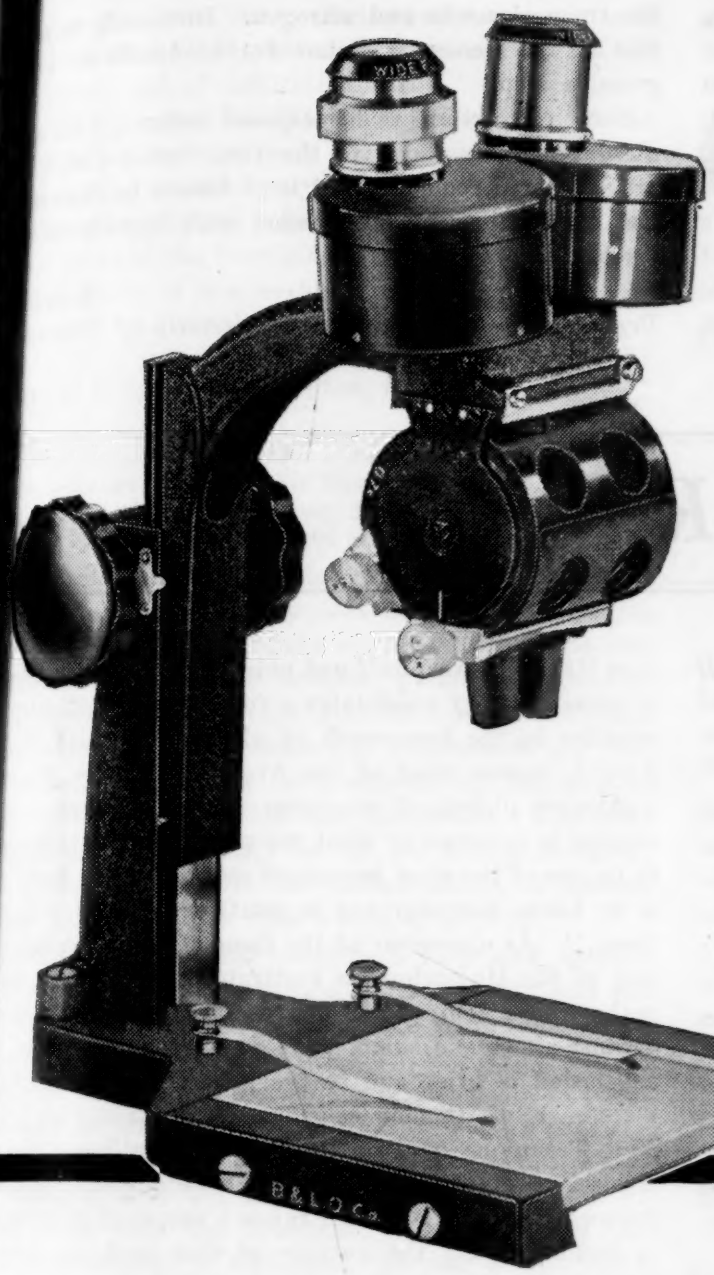
This procedure of stating the amino acid content of the protein has recently been sharply criticized by H. B. Vickery and H. T. Clarke (*Science,* 1945, 102, 454–45). They argue that since the nitrogen conversion factor for casein, edestin, and a very limited number of proteins is known, such factors should have been used and not a uniform factor based on 16 per cent of the nitrogen in the protein. Surely they are correct in insisting that the nitrogen-to-protein conversion factor, when definitely known, should be used. But, how many proteins, with known nitrogen content, have been isolated in a sufficiently pure state to make possible the erection of extensive tables on the amino acid content of proteins or foods? Not many, as compared with the number of foods and feeds.

In nutrition we are interested in the amino acid distribution in the foodstuff itself, such as wheat, meat, milk, eggs, etc., and not in the amino acid content of a single protein constituent of the foodstuff, except for fundamental studies in protein chemistry.

Consequently, Block and Bolling could do little else than follow the method they used, especially since they included in the tables such complex protein mixtures as tankage, meat scraps, fish meal, feathers, liver, grass, yeast, oats, linseed meal, etc. There are no accurate or even proposed conversion factors for such complex protein mixtures.

Historically, Armsby once proposed the term "true protein" of feeding materials for the basis of determining the protein requirement of animals. He did this because it was known that there existed in plant materials considerable unorganized nitrogen, assumed to be of non-nutritive value. The Agricultural Chemist measured the "true protein" of a feeding material, by the use of Stutzer's reagent, a copper compound supposedly effective as a precipitant of all protein nitrogen. Such a procedure is no longer followed. Yet, if one converts the nitrogen of an alfalfa hay to protein by the use of the conventional factor of 6.25, he must realize the gross error involved. There is no conversion factor for nitrogen to protein in food materials that is at all uniformly or even approximately reliable.

With this situation, what can be done? Adopt the plan of expressing the amino acids of a food or a feed material as per cent (1) of the dry material or (2) of the dry, fat-free material. We do this today for many constituents such as calcium, magnesium, etc. No attempt is made to express such constituents as per cent of the ash or of the complexes in which they exist. Use the weight of the free amino acid and not the anhydride. When the amino acid content of a food is expressed on the dry basis, it would be desirable to have the analysis accompanied by the amount of fat in the sample, especially for those products such as meat, where the fat content is extremely variable. These are the preferred methods. Or, (3) express the amino acids of a food or a feedstuff as per cent of the total nitrogen either



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on a fat and water-free basis or as the material occurs. Again use the weight of the free amino acid and not its anhydride. This procedure is in part a reversion to the elemental system so far as nitrogen is concerned, such as is now used for calcium, magnesium, potassium, phosphorus, etc., in food materials.

At one time most of these elements were expressed as the oxides such as K_2O (potash) for potassium and P_2O_5 (phosphoric acid) for phosphorus. The "oxide system" is still in vogue in the fertilizer industry except for trace elements and nitrogen. But surely the a tion of the elemental system for foodstuffs was a gressive step.

Such a procedure as is proposed under (3) still l absolute accuracy due to the fact that not all of nitrogen of a food material is of known nutritive va But the method is not clouded with hypothetical version factors.

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Book Reviews

One world or none: a report to the public on the full meaning of the atomic bomb. **Dexter Masters and Katherine Way. (Eds.) New York: Whittlesey House, McGraw-Hill, 1946. Pp. x + 79. (Illustrated.) $1.00.**

Since the publication of the Smyth report this book is perhaps the most significant which has appeared on the subject of the atomic bomb. It is a collection of skillfully edited articles written by the men who laid the scientific foundations on which the bomb was constructed; by the men who built the bomb; by those who were the official War Department inspectors of the destruction wrought by the bomb; by those who realize its implications for the world—in short, it is written *by those who know about the bomb.* Those of us who wish to live out our years in this world, who want some assurance that our children will also live out their years, can do no less than to listen to these men and ponder the message they carry.

Who are the authors of this significant book? Niels Bohr, A. H. Compton, H. H. Arnold, Hans Bethe, E. U. Condon, Albert Einstein, Irving Langmuir, Walter Lippmann, Philip Morrison, J. R. Oppenheimer, Louis Ridenour, Frederick Seitz, Harlow Shapley, Leo Szilard, Harold Urey, Eugene P. Wigner, Gale Young, and the Federation of American Scientists. *They are the men who know.*

What do they tell us, *these men who know*? Philip Morrison, one of the official War Department inspectors begins the book by giving a grim picture of the damage done at Hiroshima, and he speculates on the basis of observed facts about the damage a similar bomb might do in New York. Harlow Shapley, Harvard astronomer, next proceeds to discuss atomic energy as it operates in the sun and stars, thus providing a basis for understanding man's efforts to release this energy on earth. E. P. Wigner discusses the roots of atomic energy, explaining what atomic energy is and how it operates in a bomb, and Gale Young tells about the industrial possibilities of atomic energy. J. R. Oppenheimer, the man who directed the actual building of the bomb writes about it as "the new weapon" and points out that "the rele of atomic energy constitutes a force too revolutionary consider in the framework of old ideas." Gen. H. Arnold, former chief of the Army Air Forces, pres a sobering picture of air power in any future war. chapter is followed by what the present reviewer belie to be one of the most important sections in the book. is by Louis Ridenour and is entitled: "There is no d fense." As a member of the famous Radiation Labor tory of the Massachusetts Institute of Technology, he perhaps best equipped to discuss the problem of defen against an atomic bomb. After reviewing the facts, h conclusion is brief and to the point: THERE IS NO DE FENSE. E. U. Condon continues in a chapter on "T New Technique of Private War" by outlining the in creased possibilities opened to the saboteur and the age provocateur. If the reader raises a skeptical eyebrow, h is reminded that the authors of this book are serio scientists and not writers of scientific fiction.

Frederick Seitz and Hans Bethe attempt an estimat of how close is the danger of atomic warfare and war that it is much closer than we dream. Irving Langmui lucidly outlines the stages in an atomic arms race and th alternatives to such a race. He points out that we can and must, find a basis for amicable living with Russia and is in favor of stopping the production of atomi bombs and dismantling the plants which produce them if these steps will insure peace.

Harold Urey assumes the mantle of Jeremiah when he asks the question (and it is far from a rhetorical one): "How Does It All Add Up?" He concludes that "it all adds up to the most dangerous situation that humanity has ever faced in all history." Leo Szilard raises the problem of whether an atomic arms race can be averted by an inspection system, and Walter Lippmann examines the question of the international control of atomic energy. Albert Einstein points a way out—a way he feels is the only course, that of vesting military power in a world state. Finally, the Federation of American Scientists, in a summary of the issues, warns that survival is at stake and issues a clarion call to action.

es, survival is at stake—not merely personal and ridual survival but the survival of our nation, of r nations, and of civilization itself.

e facts assembled in this book provide a vision of atomic energy can do in a world which uses it for tructive and peaceful purposes. But these same facts t to the inescapable conclusion that while "the na- of the world can have atomic energy and much more, cannot have it in a world where war may come."

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Royal Society 1660–1940: a history of its administration under its charters. **Sir Henry Lyons, F.R.S. Cambridge: At the Univ. Press; New York: Macmillan, 1944. Pp. x + 354. (Out of print.)**

s the late Sir Henry Lyons has stated in his Introtion, this is not the complete history of the Royal iety: "This account of the way in which the Society ried on its business at different periods will provide groundwork for a fuller discussion of its influence the advancement of science; it also records the conions under which the more eminent of its Fellows rried out their researches and discoveries. The comte history of the Society has not yet been undertaken, it may well require the united efforts of several rkers to deal with so wide a field of activity."

Nevertheless, this book contains a surprising amount information about the origin of the Society and the years of science in England since its establishment. ny interesting sidelights of scientific history are inspersed between the discussions of the financial probns and administrative organization of the Society hich are its principal concern. It is amusing to learn, r example, that the Royal Society was accused of king sides with the American colonists during the evolution because it advocated the use of Benjamin ranklin's pointed lightning rods, and that the King imself tried to persuade the Society to rescind its esolution.

Although the original founders of the Royal Society ere mostly scientists who met for the purpose of critically examining new discoveries and theories, the scientific purpose of the Society was often lost sight of, and scientists were actually in the minority until 1860. Even Samuel Pepys was president (a good one, to be sure) during the two years when Newton's *Principia* was being published. Incidentally, it was Sir Isaac Newton, first man of science to be knighted, who was responsible for the fact that the Royal Society now meets on Thursdays, since he was occupied at the mint on Wednesdays (the Society's original meeting day) during the first years of his presidency. Despite the presidencies of such well-known men of science as Newton and Sir Joseph Banks, the Royal Society was more of a cultural than a scientific institution until the middle of the Nineteenth Century. Since 1860, however, the Society has become the leader of scientific thought in Great Britain and a unique institution in the world of science. Like all venerable institutions, it is sometimes slow to

change, and it is something of a shock to learn that the uncomfortable benches in use for generations were not replaced until 1939, when "others of modern type more suitable for meetings which lasted long and demanded the close attention of the audience" were installed.

As treasurer of the Royal Society for many years, Sir Henry Lyons had access to its records and was well qualified to write its administrative history. The great wealth of information in this book concerning the finances and administration of the Royal Society make it particularly useful to specialists in the history of science. Inasmuch as there has been no comprehensive history of the Society for a hundred years, the book should also be of interest to those who are not specialists for it is much more than a treasurer's report. Each chapter has a useful short bibliography and there is an excellent index. It is to be regretted that this book was published in such a small edition that it is already out of print.

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B-Chloroethyl Amines and Sulfides

(Continued from p. 415.)

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[1] The majority of the references cited above are to classified documents which are not generally available. Reference is therefore made to authors and the time at which their work was conducted. Those references preceded by an asterisk refer to unpublished British work.